UNITED STATES PATENT AND TRADEMARK OFFICE

———————————

BEFORE THE PATENT TRIAL AND APPEAL BOARD

———————————

Apotex Inc. and Apotex Corp.,
Petitioners

v.

ABRAXIS BIOSCIENCE, LLC,
Patent Owner

———————————

Case IPR2018-00152
Patent 7,820,788 B2

———————————

**DECLARATION OF CORY J. BERKLAND, Ph.D.
IN SUPPORT OF PETITION FOR *INTER PARTES* REVIEW**

# TABLE OF CONTENTS

## EXHIBITS CITED

| EX | Description |
|---|---|
| 1001 | Desai et al., U.S. Patent No. 7,820,788 B2, "Compositions and Methods of Delivery of Pharmacological Agents" (issued Oct. 26, 2010) (the "'788 patent") |
| 1004 | Kadima et al., WO 00/06152, "Pharmaceutically Acceptable Composition Comprising an Aqueous Solution of Paclitaxel and Albumin" (published Feb. 10, 2000) ("Kadima") |
| 1005 | Liversidge et al., U.S. Patent No. 5,399,363, "Surface Modified Anticancer Nanoparticles" (issued Mar. 21, 1995) ("Liversidge") |
| 1006 | Desai et al., WO 1999/000113, "Novel Formulations of Pharmacological Agents, Methods for the Preparation thereof and Methods for the Use thereof" (published Jan. 7, 1999) ("Desai") |
| 1007 | Li et al., "Fluorescein Binding to Normal Human Serum Proteins Demonstrated by Equilibrium Dialysis," Arch Ophalmol. vol. 100, 484–87 (March 1982) |
| 1009 | FDA Guideline on Sterile Drug Products Produced by Aseptic Processing (June 1987, reprinted June 1991 and Feb. 1997) |
| 1010 | EMEA Guidance on Manufacture of the Finished Dosage Form (April 1996) |
| 1011 | *Elan Pharma Int'l Ltd. v. Abraxis BioScience, Inc.*, Judgment and Verdict Form, No. 06-438-GMS, Dkt. 614 (D. Del. June 16, 2008) |
| 1017 | Damascelli, B et al. "Intraarterial chemotherapy with polyoxyethylated castor oil free paclitaxel, incorporated in albumin nanoparticles (ABI-007)," Cancer 2001 Nov; 92(10):2592–2602 ("Damascelli") |
| 1018 | Ibrahim et al., "Phase I and pharmacokinetic study of ABI-007, a Cremophor-free, protein-stabilized, nanoparticle formulation of paclitaxel," Clin Cancer Res. 2002 May; 8:1038–44 ("Ibrahim") |
| 1023 | U.S. Application No. 11/553,339, Declaration of Neil P. Desai Pursuant to 37 C.F.R. § 1.132 (dated Apr. 14, 2010) |

I, Cory J. Berkland, Ph.D., hereby declare as follows:

## I. INTRODUCTION

1. I am currently appointed as the Solon E. Summerfield Distinguished Professor in the Department of Pharmaceutical Chemistry and the Department of Chemical and Petroleum Engineering at the University of Kansas. I have been retained by Petitioners Apotex Inc. and Apotex Corp. ("Apotex") in connection with its request for *inter partes* review of U.S. Patent No. 7,820,788 ("the '788 patent"). A copy of the '788 patent has been marked EX1001. I have reviewed and am familiar with the '788 patent. Generally, it describes and claims pharmaceutical compositions comprising the anticancer drug paclitaxel bound to the protein albumin and formulated as nanoparticles, and methods of using such compositions to treat diseases including cancer.

2. I have been asked to provide my opinions regarding the patentability of claims 1–12 of the '788 patent (the "challenged claims"). This declaration includes a discussion of my background and qualifications, the legal standards used in my analysis, an overview of the '788 patent from the perspective of a person of ordinary skill in the art at the time that the patent was filed (a "skilled artisan"), and my opinions regarding the patentability of the challenged claims.

3. I am being compensated for my work in this proceeding at my standard hourly consulting rate of $500.00 per hour. My compensation is in no way

contingent on the substance of my opinions or the outcome of this proceeding.

4.      As set forth more fully below, it is my opinion that claims 1–9 and 11–12 of the '788 patent are anticipated by a previously published international patent application, WO 99/00113 to Desai et al. ("Desai") (EX1006). Additionally, it is my opinion that claims 1–12 would have been obvious to a skilled artisan in view of Desai, either alone or in combination with another previously published international patent application, WO 00/06152 to Kadima et al. ("Kadima") (EX1004), and a previously issued patent, U.S. Patent No. 5,399,363 to Liversidge et al. (EX1005). The bases for my opinions are set forth in this declaration.

## II.      BACKGROUND AND QUALIFICATIONS

5.      I received a B.S. in Chemical Engineering from Iowa State University in December 1998, and an M.S. in Chemical Engineering from the University of Illinois in May 2001. I received a Ph.D. in Chemical and Biomolecular Engineering from the University of Illinois in May 2003. From 2004 to 2009, I was an Assistant Professor in the Department of Chemical and Petroleum Engineering and the Department of Pharmaceutical Chemistry at The University of Kansas. Since 2009, I have been a Professor in these two departments with tenure.

6.      My areas of expertise include drug formulation using particulates and powders, microencapsulation of pharmaceuticals, and controlled-release drug delivery. Through collaborations with industrial and academic partners, and close re-

lationships with other experts in controlled release, I have developed considerable expertise in the formulation and characterization of particles and powders.

7. The primary focus of my research has been the design and analysis of drug delivery approaches for improving the performance of therapeutic agents. I have worked on particles and aspects of pharmaceutical formulation and delivery, including nanoparticle formulations, since 1997. Among other areas, I have conducted research aimed to elucidate important parameters (*e.g.*, particle size, morphology, surface chemistry) for controlling the release or dissolution of drugs.

8. My research group at the University of Kansas currently works on formulation approaches designed to modify drug dissolution kinetics and to control drug release rates. My work has encompassed microencapsulation, nanoparticle formulations, and polymers for delivering small molecules, proteins, and DNA. I have expertise in analyzing the performance of such formulations and in applying mathematical models to elucidate the underlying phenomena controlling the dissolution or release of such drugs. I have also designed and taught classes on drug delivery that focus primarily on drug transport in pharmaceutical formulations and through different biological barriers in the human body.

9. I have been a member of various professional organizations, including the American Institute of Chemical Engineers, the American Chemical Society, the American Association of Pharmaceutical Scientists, and the Controlled Release

Society. I am a Fellow of the American Institute of Medical and Biological Engineering, and have received honors and awards from various national and international organizations, including the Leading Light Award from the University of Kansas, the Nagai Foundation Distinguished Lectureship, and the Controlled Release Society Young Investigator Award. Other awards and honors I have received are listed in my CV, which is attached as the Appendix to this declaration.

10.    I have sat on editorial and scientific advisory boards of scientific journals including Therapeutic Delivery, the Journal of Pharmaceutical Sciences, and the Journal of Pharmaceutical Innovation.

11.    I have published on such topics as drug delivery, nanoparticle formulation, surface modification, controlled release, and biomaterials. I have published approximately 150 articles in peer-reviewed journals, three book chapters, and have been named as a co-inventor on more than 50 U.S. patents or applications.

12.    I have served as a consultant in the area of drug formulation and delivery for U.S. and international companies, and have testified as an expert witness in the area of drug formulation and delivery in several trials. My publications, including publications authored within the past ten years, are listed in my CV.

13.    I have been involved in the development of numerous pharmaceutical products, both in my capacity at the University of Kansas and as a company founder. For instance, I am a co-founder of four companies: Orbis Biosciences,

Inc., Savara Pharmaceuticals, Inc., Orion BioScience, Inc., and Bond Biosciences, Inc. I am the acting Chief Scientific Officer at Orbis Biosciences. Orbis develops controlled-release delivery systems, including parenteral, injectable formulations. I was also a Member of the Scientific Advisory Board and the former Chief Technology Officer for Savara Pharmaceuticals, Inc. in Austin, Texas. Savara specializes in the development of pulmonary drug products. I am also the Chairperson of the Board of Directors of Orion BioScience, Inc., which develops injectable immune-specific therapies for autoimmune diseases.

## III. LEGAL STANDARDS USED IN MY ANALYSIS

14. I am not a patent attorney, nor have I independently researched patent law. Counsel for Petitioners have explained certain legal standards to me that I have relied upon in forming my opinions set forth in this Declaration.

### A. Prior art

15. I have been informed that the law provides certain categories of information, known as prior art, that may be used to render patent claims anticipated or obvious. The reference materials I discuss in this declaration are prior art at least because they would have been available to members of the public as of December 9, 2002, and are relevant to the subject matter of the '788 patent. The references I discuss herein are from the same field of endeavor as the claimed invention (even if they address a different problem), and/or are reasonably pertinent to the problem

faced by the inventor (even if they are not in the same field of endeavor as the claimed invention).

**B.      Person of ordinary skill in the art**

16.      I understand that U.S. provisional application no. 60/432,317, to which the '788 patent claims priority, was filed on December 9, 2002, as stated on the front of the patent under the title "Related U.S. Application Data." For purposes of my analysis, and without offering any opinion as to whether the '788 patent's claim to priority is valid or appropriate, I have used the December 9, 2002 date as the relevant date for my analysis of the prior art.

17.      I understand that the assessment of the patentability of the claims of the '788 patent must be undertaken from the perspective of a hypothetical person of ordinary skill in the art of the earliest priority date of the '788 patent, *i.e.*, a skilled artisan. The person of ordinary skill in the art is a hypothetical person who is presumed to have known the relevant art as of the effective filing date. Factors that may be considered in determining the level of ordinary skill in the art may include, (i) type of problems encountered in the art, (ii) prior art solutions to those problems, (iii) rapidity with which innovations are made, (iv) sophistication of the technology, and (v) educational level of active workers in the field. I understand that in a given case, every factor may not be present, and one or more factors may predominate.

18.     I understand that the hypothetical person having ordinary skill in the art to which the claimed subject matter pertains would, of necessity have the capability of understanding the scientific and engineering principles applicable to the pertinent art. I further understand that a person of ordinary skill in the art is also a person of ordinary creativity, not an automaton. In many cases a person of ordinary skill will be able to fit the teachings of multiple patents or prior art references together like pieces of a puzzle.

19.     Based on these factors, my knowledge and expertise, and the prior art to the '788 patent (*i.e.*, publications before December 9, 2002), it is my opinion that a skilled artisan would include a person with an advanced degree in chemistry, chemical engineering, pharmaceutics, pharmacy, or a related discipline, and/or having experience formulating compounds for use in pharmaceutical compositions, including nanoparticle suspensions, for several years. Further, it is my opinion that the skilled artisan would know how to evaluate potential drug therapies for *in vitro* and *in vivo* activity, including with biological assays.

### C.     Anticipation

20.     I have been informed that a claim is not patentable if a single prior art reference describes every element of the claim, either expressly or inherently, to a skilled artisan. I understand that this principle is called "anticipation." I have also been informed that, to anticipate a patent claim, the prior art reference does not

need to use the same words as the claim. However, it must describe the requirements of the claim with sufficient clarity that a skilled artisan would have been able to make and use the claimed invention based on that single prior art reference.

21. In addition, I have been informed and understand that, in order to establish that an element of a claim is "inherent" in the disclosure of a prior art reference, it must be clear to one skilled in the art that the missing element is an inevitable part of what is explicitly described in the prior art reference, and that it would have been recognized as necessarily present by a skilled artisan.

**D. Obviousness**

22. I have been informed that, even if every element of a claim is not found explicitly or implicitly in a single prior art reference, the claim may still be unpatentable if the differences between the claim and the prior art are such that the claim as a whole would have been obvious to a skilled artisan at the time the invention was made. For purposes of obviousness, I understand that a skilled artisan may rely on a single prior art reference, or multiple references in combination.

23. I have been informed that the following four factors are considered when determining whether a patent claim would have been obvious to a skilled artisan: (a) the level of ordinary skill in the art; (b) the scope and content of the prior art; (c) the differences between the prior art and the claim; and (d) any "secondary considerations" tending to prove nonobviousness. These secondary considerations,

which I understand are also called "objective indicia" or "objective evidence," may include factors such as: (i) the invention's satisfaction of a long-felt unmet need in the art; (ii) unexpected results of the invention; (iii) skepticism of the invention by experts; (iv) teaching away from the invention in the prior art; (v) commercial success of an embodiment of the invention; and (vi) praise by others for the invention. I have also been informed that there must be an adequate nexus or connection between the evidence that is the basis for an asserted secondary consideration and the scope of the invention claimed in the patent.

24.    I understand that when every limitation of a claim is disclosed in the cited prior art references, the question of obviousness turns on whether a hypothetical person of ordinary skill in the art would have been motivated to combine those teachings to derive the claimed subject matter with a reasonable expectation of success. Further, I understand that obviousness does not require absolute predictability. Only a reasonable expectation that the beneficial result will be achieved is necessary to show obviousness.

25.    I have been informed that a claimed invention can be rendered obvious by the combination of teachings in the prior art even if there is no explicit teaching to combine them. Instead, any problem known in the field at the time of the alleged invention can provide a sufficient rationale to combine the elements of the prior art in the manner claimed in the patent.

26.    I have been informed that examples of sufficient rationales for establishing obviousness include the following:

- combining prior art elements according to known methods to yield predictable results;

- substituting known elements for other known elements to obtain predictable results;

- using a known technique to improve similar devices, methods, or products in the same way;

- choosing from a finite number of identified, predictable solutions that would be obvious to try; and

- providing some teaching, suggestion, or motivation to modify the prior art reference or to combine teachings in prior art references to arrive at the claimed invention.

27.    I understand that where there is a range disclosed in the prior art, and the claimed invention falls within that range, the burden of production falls upon the patentee to come forward with evidence that (1) the prior art taught away from the claimed invention; (2) there were new and unexpected results relative to the prior art; or (3) there are other pertinent secondary considerations. For purposes of this analysis, I understand that a prior art reference does not "teach away" from a claimed invention unless it criticizes, discredits, or otherwise discourages investi-

gation into the invention claimed.

## IV. THE '788 PATENT

### A. The alleged invention

28. The '788 patent is entitled "Compositions and Methods of Delivery of Pharmacological Agents," and generally relates to pharmaceutical compositions comprising paclitaxel and a pharmaceutically acceptable carrier, such as human serum albumin, and methods of treating diseases, including cancer, by administering such compositions. EX1001, cover, abst.

29. As background, the '788 patent explains that "many drugs for parenteral use, especially those administered intravenously, cause undesirable side effects" that are "administration related." *Id.* at 1:27–31. "Many of these drugs," the patent explains, "are insoluble in water, and are thus formulated with solubilizing agents, surfactants, solvents, and/or emulsifiers that are irritating, allergenic, or toxic when administered to patients." *Id.* at 1:31–34. The patent goes on to state that known "drugs that exhibit administration-associated side effects include, for example, Taxol (paclitaxel)." *Id.* at 1:52–54.

30. Paclitaxel, which as the '788 patent acknowledges is sold under the brand name Taxol, was known to be "active against carcinomas of the ovary, breast, lung, esophagus and head and neck." *Id.* at 4:31–33. "Taxol, however, has been shown to induce toxicities associated with administration." *Id.* at 4:33–34.

"Because paclitaxel is poorly soluble in water, cremophor [*i.e.*, polyethoxylated castor oil] typically is used as a solvent, requiring large infusion volumes and special tubing and filters." *Id*. at 4:37–39. "Cremophor is associated with side effects that can be severe, including anaphylaxis and other hypersensitivity reactions that can require pretreatment" with various drugs. *Id*. at 4:39–43.

31.     The '788 patent discloses compositions and methods that supposedly reduce or eliminate the cremophor-related side effects that had been associated with the administration of paclitaxel. *Id*. at 2:34–45. Specifically, the patent discloses compositions comprising paclitaxel together with a pharmaceutical carrier, which is preferably human serum albumin. *Id*. at 2:54–58. "Preferably, the formulation is essentially free of cremophor," thus avoiding its "side effects that can be severe." *Id*. at 11:67–12:6.

32.     Human serum albumin is a highly soluble protein, and is the most abundant protein in human blood plasma. *Id*. at 5:15–18. The '788 patent acknowledges that the intravenous use of human serum albumin solution was known in the art. *Id*. at 5:21–22. Human serum albumin has "multiple hydrophobic binding sites," allowing it to bind to hydrophobic, water-insoluble drugs like paclitaxel. *Id*. at 5:29–46. The '788 patent theorizes that "the inclusion of proteins such as albumin in the inventive pharmaceutical compositions results in a reduction in side effects associated with administration of the pharmaceutical composi-

tion that is due, at least in part, to the binding of human serum albumin to any free drug that is present in the composition." *Id.* at 5:52–58.

33. The '788 patent states generally that "[t]he amount of albumin included in the pharmaceutical composition of the present invention will vary depending on the pharmaceutical active agent, other excipients, and the route and site of intended administration," so long as "the amount of albumin included in the composition is an amount effective to reduce one or more side effects the active pharmaceutical agent due to the [ ] administration of the inventive pharmaceutical composition to a human." *Id.* at 5:59–66. In general, "compositions with lower amounts of albumin are preferred as this can greatly reduce cost," among other alleged reasons. *Id.* at 35:34–36.

34. The '788 patent discloses a wide range of albumin-paclitaxel ratios for its compositions: "Exemplary ranges for protein-drug preparations are protein to drug ratios (w/w) of 0.01:1 to about 100:1. More preferably, the ratios are in the range of 0.02:1 to about 40:1." *Id.* at 11:58–61. As the patent explains, "the ratio of protein to pharmaceutical agent will have to be optimized for different protein and pharmaceutical agent combinations." *Id.* at 11:61–63. The patent then discloses certain "preferred" ranges, and concludes by stating: "Most preferably, the ratio is about 1:1 to about 9:1." *Id.* at 11:66–67.

35. The patent includes examples of various pharmaceutical composi-

tions. None of these examples discloses a formulation with an albumin-paclitaxel ratio of about 9:1. The only examples that mention the ratio of albumin to paclitaxel disclose ratios of 27:1, 4.5:1, and 10:1, and each of these examples makes clear that the ratio is calculated based on the ingredients used to make the composition, and/or that the ratio of the final composition remains the same as the ratio of the starting ingredients. *See id.* at 35:44–47 (Example 47); 36:10–13 (Example 48); 36:42–61 (Example 49).

36.     For instance, Example 47 states: "30 mg of paclitaxel was dissolved in 3.0 ml methylene chloride.  The solution was added to 27.0 ml of human serum albumin solution (3% w/v) (corresponding to a ratio of albumin to paclitaxel of 27)." *Id.* at 35:44–47. Likewise, Example 48 states:  "300 mg of paclitaxel was dissolved in 3.0 ml methylene chloride.  The solution was added to 27 ml of human serum albumin solution (5% w/v) (corresponding to a ratio of albumin to paclitaxel of 4.5)." *Id.* at 36:10–13. In both of these examples, the recited ratio is based on the starting materials used to make the composition.

37.     Similarly, Example 49 states: "135 mg of paclitaxel was dissolved in 3.0 ml methylene chloride.  The solution was added to 27 ml of human serum albumin solution (5% w/v)." *Id.* at 36:42–44. In other words, 135 mg of paclitaxel was combined with 1,350 mg of albumin (27 ml of 5% w/v solution), corresponding to a 10:1 ratio. After reciting several process steps, Example 49 states: "The

calculated ratio (w/w) of albumin to paclitaxel in this invention composition is approximately 10." *Id.* at 36:42–61. Apparently, therefore, the albumin-paclitaxel ratio of Example 49 was either "calculated" based on the starting materials, or measured after the process steps were completed, at which point the ratio remained the same as the ratio of starting materials.

38.     There is no suggestion in the '788 patent that the ratio of albumin to paclitaxel materially changes during the manufacturing process. Nor is there any disclosed assay or discussion of how to measure or predict the ratio of albumin to paclitaxel in the final pharmaceutical composition.

39.     The '788 patent provides that the claimed compositions can be prepared as nanoparticles. *Id.* at 9:33–35. Several examples in the patent describe nanoparticle formulations. In each one, the example provides that "the typical average diameter" of the particles ranges from "50–220 nm (Z-average, Malvern Zetasizer)." *See id.* at 14:62–63 (Example 1); 15:23–25 (Example 2); 16:1–3 (Example 4); 16:28–31 (Example 5); 16:58–61 (Example 6); 17:22–24 (Example 7); 17:58–60 (Example 8); 18:26–28 (Example 9); 18:58–61 (Example 10); 19:19–21 (Example 11); 19:44–45; (Example 12); 19:63–65 (Example 13); 20:21–23 (Example 14); 35:57–59 (Example 47); 36:23–25 (Example 48); 36:54–56 (Example 49). The "Z-average" is one possible measurement of particle diameter, and a "Malvern Zetasizer" is a particular device that is capable of determining that measurement.

## B. Challenged claims

40. Claim 1 of the '788 patent is directed to a pharmaceutical composition for injection comprising paclitaxel and albumin, formulated as particles having a particle size of less than about 200 nm, "wherein the weight ratio of albumin to paclitaxel in the composition is about 1:1 to about 9:1."

41. Claim 2 depends from claim 1 (*i.e.*, it incorporates all the limitations of claim 1) and further requires that the albumin is human serum albumin.

42. Claim 3 depends from claim 1 and further requires that the composition is free of Cremophor.

43. Claim 4 is directed to a method of treating cancer, arthritis, or restenosis by administering the composition of claim 1.

44. Claim 5 depends from claim 4 and requires that the disease treated is cancer.

45. Claim 6 depends from claim 4 and requires that the disease treated is arthritis.

46. Claim 7 depends from claim 4 and requires that the disease treated is restenosis.

47. Claim 8 depends from claim 4 and further requires that the composition is administered "intravenously, intraarterially, intrapulmonarily, orally, by inhalation, intravesicularly, intramuscularly, intratracheally, subcutaneously, intraoc-

ularly, intrathecally, or transdermally."

48.    Claim 9 depends from claim 8 and specifies that the method of administration is intravenous.

49.    Claim 10 depends from claim 1 and specifies that "the ratio (w/w) of albumin to the paclitaxel in the pharmaceutical composition is about 1:1 to about 5:1."

50.    Claim 11 depends from claim 1 and specifies that "the ratio (w/w) of albumin to the paclitaxel in the pharmaceutical composition is 1:1 to 9:1."

51.    Claim 12 depends from claim 1 and specifies that "the ratio (w/w) of albumin to the paclitaxel in the pharmaceutical composition is about 9:1."

## C.    Claim construction

52.    Counsel for Petitioners has informed me that in proceedings before the Patent Office, the claims of a patent must be construed to have their broadest reasonable interpretation in light of the specification and prosecution history of the patent. Furthermore, I understand that, in general, the broadest reasonable interpretation of the claims of a patent corresponds to their plain and ordinary meaning from the perspective of a skilled artisan.

53.    In my opinion, a skilled artisan would have understood that the broadest reasonable interpretation of the terms "weight ratio of albumin to paclitaxel in the composition" and "ratio (w/w) of albumin to the paclitaxel in the pharmaceuti-

cal composition" in the challenged claims includes the ratio of albumin to paclitaxel in the starting ingredients used to make the composition. A skilled artisan reading the '788 patent would have understood that the desired ratio of albumin to paclitaxel could be determined based on the starting ingredients because, as I discussed above, that is how the ratio was determined in Examples 47, 48, and 49, which are the only examples that mention an albumin-paclitaxel ratio, and no other method of calculating the ratio is provided in the patent.

54.     It is also my opinion that a skilled artisan would have understood that the term "less than about 200 nm" in the challenged claims includes particle sizes of 220 nm or less, measured as the Z-average diameter using a Malvern Zetasizer. As I noted above, every example in the '788 patent that mentions particle size refers to the average diameter of the particles, measured as the Z-average using a Malvern Zetasizer, and covers a typical average diameter range up to 220 nm. Moreover, it was understood in the relevant art as December 2002 that the word "about" generally includes sizes above and below 10% of the stated particle size. Thus, a skilled artisan would have understood "about 200 nm" to include 220 nm or less, which is 10% above the stated size of 200 nm.

## V.     THE PRIOR ART

### A.     Desai (EX1006)

55.     Desai was published on January 7, 1999, and is therefore prior art to

the '788 patent. EX1006, 1.

56. Desai "relates to methods for the production of particulate vehicles for the intravenous administration of pharmacologically active agents, as well as novel compositions produced thereby." *Id.* at 3. "In a particular aspect, the invention relates to methods for the *in vivo* delivery of substantially water insoluble pharmacologically active agents (*e.g.*, the anticancer drug Taxol®)," *i.e.*, paclitaxel. *Id.* A "preferred" embodiment of Desai comprises "extremely small particles" that make up a "drug delivery system in either liquid form or in the form of a redispersible powder," providing "pure drug particles coated with a protein." *Id.*

57. Like the '788 patent, Desai describes the "anticancer effects" of paclitaxel, noting that Taxol has been called "the new anticancer wonder-drug." *Id.* at 7. "The poor aqueous solubility of Taxol, however, presents a problem for human administration." *Id.* "Accordingly, currently used Taxol formulations require a cremaphor to solubilize the drug," which "has been linked to severe hypersensitivity reactions … and consequently requires premedication of patients." *Id.*

58. Desai states that "it is an object of this invention to deliver pharmacologically active agents (*e.g.*, Taxol, taxane, Taxotere, and the like) in unmodified form in a composition that does not cause allergic reactions due to the presence of added emulsifiers and solubilizing agents, as are currently employed in drug delivery," and "[i]t is a further object of the present invention to deliver pharmacologi-

cally active agents in a composition of microparticles or nanoparticles." *Id.* at 22.

"It is yet another object of [Desai] to provide methods for the formation of submicron particles (nanoparticles) of pharmacologically active agents," including "methods [that] use proteins as stabilizing agents." *Id.*

59.     According to Desai, its inventors "discovered that substantially water insoluble pharmacologically active agents can be delivered in the form of microparticles or nanoparticles that are suitable for parenteral administration in aqueous suspension. This mode of delivery obviates the necessity for administration of substantially water insoluble pharmacologically active agents (*e.g.*, Taxol) in an emulsion containing, for example, ethanol and polyethoxylated castor oil [*i.e.*, Cremophor]," the "disadvantage of such known compositions [being] their propensity to produce allergic side effects." *Id.* at 23.

60.     In Desai's compositions, "proteins (*e.g.*, human serum albumin) are employed as a stabilizing agent." *Id.* Desai teaches "a drug delivery system in which part of the molecules of pharmacologically active agent are bound to the protein (*e.g.*, human serum albumin)," and "contained within nanoparticles coated by protein." *Id.* at 24. In this system, "advantage is taken of the capability of human serum albumin to bind [to] Taxol," and "[s]ince albumin is present on the colloidal drug particles … , formation of a colloidal dispersion which is stable for prolonged periods is facilitated." *Id.* at 25.

61.     Desai "further provides a method for the reproducible formation of unusually small nanoparticles (less than 200 nm diameter)." *Id.* at 23. This size corresponds to Desai's "preferred embodiment," in which "the average diameter of the ... particles is no greater than about 200 nm." *Id.* at 38.

62.     Desai explains that the "submicron particles" of the composition can be provided "in powder form, which can easily be reconstituted in water or saline." *Id.* at 25–26. "The powder is obtained after removal of water by lyophilization," *i.e.*, by freeze-drying, which "produces a sterile solid formulation useful for intravenous injection." *Id.* at 26.

63.     An exemplary formulation of Desai is "Capxol," which is described as a "cremophor-free formulation of the anticancer drug paclitaxel." *Id.* at 27. "Capxol™ is a lyophilized powder for reconstitution and intravenous administration," and "[w]hen reconstituted with a suitable aqueous medium ... , Capxol™ forms a stable colloidal solution of paclitaxel." *Id.* at 28. The "preferred range" of particle sizes in Capxol is "20–400 nm." *Id.* "The two major components of Capxol™ are unmodified paclitaxel and human serum albumin (HSA)." *Id.*

64.     In certain tissues, "Capxol may be utilized to treat cancers ... with a higher efficacy than Taxol," whereas for "other tissues ... Capxol is expected to maintain anticancer activity at least equal to that of TAXOL." *Id.* at 30. Capxol's formulation also allows "increased anticancer activity for longer periods with simi-

lar doses of paclitaxel." *Id*. at 31. In general, Desai states that it is an "object of the present invention to provide a new formulation of paclitaxel that localizes paclitaxel in certain tissues, thereby providing higher anticancer activity at these sites." *Id*. at 35.

65. According to Desai, "[e]ach vial of Capxol™ contains 30 mg of paclitaxel and approximately 400 mg of human serum albumin," which corresponds to a 13.3:1 ratio of albumin to paclitaxel. *Id*. at 38.

66. Desai also states that Capxol is "produced by the method of Example 1," in the sense that "[t]he nanoparticles are prepared by high pressure homogenization of a solution of USP human serum albumin and a solution of paclitaxel in an organic solvent," which is subsequently "sterile filtered and lyophilized to obtain Capxol™." *Id*. at 38–39.

67. However, while Example 1 generally describes the process of preparing albumin-paclitaxel nanoparticles by high-pressure homogenization, it does not specifically describe a method limited to producing a sterile-filtered composition with an albumin-paclitaxel ratio of 13.3:1, or any product containing 400 mg of albumin, such as Capxol. Rather, Example 1 specifically describes a method in which 30 mg of paclitaxel is combined with 27.0 ml of human serum albumin solution at a concentration of 1% (w/v), which corresponds to 270 mg of albumin, *i.e.*, a 9:1 ratio of albumin to paclitaxel. *Id*. at 62. Example 1 provides that "the typical

diameter of the resulting paclitaxel particles was 160–220 (Z-average, Malvern Zetasizer)." *Id.* at 63. Example 1 further provides that the composition was lyophilized (*i.e.*, freeze-dried) and "could be easily reconstituted to the original dispersion by addition of sterile water or saline." *Id.* "The particle size after reconstitution was the same as before lyophilization." *Id.* Example 1 does not recite a sterile filtration step.

68.     A skilled artisan would have understood that the process of making Capxol specifically, which is sterile-filtered, has an albumin-paclitaxel ratio of 13.3:1, and is provided in vials of 30 mg paclitaxel and 400 mg of human serum albumin, is more narrowly described in Example 16, which is titled, "Summary of the Presently Preferred Manufacturing Process: Starting with 1 Gram Paclitaxel as the BDS." *Id.* at 75.

69.     In the method of Example 16, a 3% solution of human serum albumin is made from 51.7 ml of 25% albumin and 379.3 ml of water, which corresponds to 431 ml of 3% albumin, or 12,930 mg of albumin. *Id.* at 75. Example 16 uses 1 g (*i.e.*, 1,000 mg) of paclitaxel, which results initially in a 12.93:1 ratio of albumin to paclitaxel. *Id.* at 75. The resulting suspension is then sterile filtered using a 0.2 micron (*i.e.*, 200 nm) filter before being filled into vials containing 30 mg of paclitaxel each, and then lyophilized. *Id.* at 75-77.

70.     Notably, Example 4, which describes a similar step of sterile filtra-

tion, states that approximately "97% of the Taxol [*i.e.*, paclitaxel] was recovered after filtration." *Id.* at 65. Thus, as applied to Example 16, one would expect to recover approximately 97% of the paclitaxel after sterile filtration, thereby raising the 12.93:1 ratio of albumin to paclitaxel in the starting materials of Example 16 to 13.3:1, *i.e.*, the ratio of Capxol as disclosed in Desai.

71.     Aside from disclosing a 9:1 ratio of albumin to paclitaxel in Example 1 and a 13.3:1 ratio in Example 16 and for Capxol, additional examples in Desai confirm that other ratios can also be used.  For instance, in Example 4, the composition was prepared from 30 mg of paclitaxel and 29.4 ml of 1% w/v albumin.  *Id.* These ingredients correspond to a ratio of albumin to paclitaxel of 294 mg to 30 mg, *i.e.*, 9.8:1. *Id.* Likewise, in Example 5, the composition was prepared from 225 mg paclitaxel and 97.0 ml of 3% w/v human serum albumin.  *Id.* at 66.  These ingredients correspond to a ratio of albumin to paclitaxel of 2910 mg to 225 mg, *i.e.*, 12.9:1. *Id.*

72.     In addition, Desai discloses a preferred range of albumin concentrations for producing albumin-paclitaxel formulations: "Protein is added at a concentration in the range of about 0.05 to 25% (w/v), more preferably in the range of about 0.5% – 5% (w/v)." *Id.* at 50. Although this range is disclosed as part of the description of a process for forming micron-sized particles (*id.* at 49), the same range applies to the process "for the formation of unusually small submicron parti-

cles (nanoparticles), *i.e.*, particles which are less than 200 nanometers in diameter." *Id.* at 52; *see id.* at 53 (explaining that in the process of forming nanoparticles, "human serum albumin … as described above [*i.e.*, as described at page 48] is dissolved in aqueous media").

73.　　Thus, although Example 1 of Desai exemplifies a process utilizing a 1% (w/v) concentration of albumin, Desai discloses that processes using lower concentrations of albumin, including concentrations as low as 0.5% (w/v), are also preferred. *Compare id. with* 62. As Desai explains, moreover, the examples such as Example 1 are "non-limiting." *Id.* at 62.

74.　　Desai also discloses reasons for increasing the paclitaxel concentration of existing formulations. As Desai explains, the need to combine Taxol with cremaphor as a solvent meant that the paclitaxel in the formulation was highly diluted, which "results in large volumes of infusion … up to 1 liter and infusion times ranging from 3 hours to 24 hours." *Id.* at 7–8. Taxol's "long infusion duration is inconvenient for patients, and is expensive due to the need to monitor the patients for the entire 6 to 24-hour infusion duration." *Id.* at 17. Thus, Desai explains that "[i]t is desirable to reduce these infusion volumes, by developing formulations of paclitaxel that are stable at higher concentrations so as to reduce the time of administration." *Id.* at 21. By "allow[ing] for the delivery of high doses of the pharmacologically active agent in relatively small volumes," a formulation can

"minimize[] patient discomfort at receiving large volumes of fluid and minimize[] hospital stay." *Id*. at 54.

75.     More specifically, Desai discloses that it is desirable "to obtain a higher loading of drug into the crosslinked protein shell," *i.e.*, increasing the amount of paclitaxel in the particle relative to the albumin shell, thereby reducing the albumin-paclitaxel ratio. *Id*. at 79.

76.     Further, in addition to reducing infusion volumes and increasing patient tolerability, Desai discloses that "[t]here is evidence in the literature that higher doses of paclitaxel result in a higher response rate." *Id*. at 19.

77.     The examples of Desai also describe methods of using the disclosed albumin-paclitaxel formulations. For instance, Example 45 is a pilot study showing the effectiveness of albumin-paclitaxel nanoparticles against mammary tumors. *Id*. at 122–23. Similarly, Example 46 discloses a method of treating rheumatoid arthritis, and Example 47 discloses a method of treating artery restenosis. *Id*. at 123-27. Example 58 compares the effectiveness of albumin-paclitaxel nanoparticles to Taxol in treating mammary tumors. *Id*. at 140–42. In Example 40, which shows the tissue location of Capxol compared to Taxol, the inventors of Desai conclude that Capxol may be more effective in the treatment of cancers of the prostate, pancreas, kidney, lung, heart, bone, and spleen at equivalent levels of paclitaxel. *Id*. at 146.

**B.     Kadima (EX1004)**

78.     Kadima was published on February 10, 2000, and is thus prior art to the '788 patent. EX1004, 1.

79.     Kadima generally relates to pharmaceutical compositions comprising paclitaxel and serum albumin, wherein "[a]t least 70% of the paclitaxel is bound to serum albumin, [and] the ratio of paclitaxel to albumin is at least about 1:5," *i.e.*, an albumin-paclitaxel ratio of about 5:1. *Id.*

80.     Like Desai, Kadima teaches that "the highest concentrations of paclitaxel" achievable are desirable, as "[t]his results in the smallest volumes for administration or lyophilization/reconstitution, which enables more rapid admin-istration, if desired." *Id.* at 13.

81.     Kadima teaches that higher concentrations of paclitaxel can be ob-tained by adjusting the "ratio of paclitaxel:albumin" and the "concentration of paclitaxel in the albumin solution." *Id.*; *see* 12–13 (discussing the desirability of lower ratios of albumin to paclitaxel).

82.     While noting that albumin is an effective stabilizer, Kadima observes that "[a]lbumin is a cost-limiting component for use in drug stabilization." *Id.* at 10. Kadima thus emphasizes the importance of providing a "commercially feasible method for using a serum albumin to administer paclitaxel." *Id.* at 33. Kadima explains that one challenge to achieving this goal is that "[a]lbumin is an expensive

ingredient." *Id.*

83.    Kadima illustrates the impact of the albumin-paclitaxel ratio on the
cost of producing a pharmaceutical composition with the following chart:

| Molar ratio | Paclitaxel (mg) | HSA (g) | Paclitaxel Cost | HSA Cost[1] | Ingredients Total Cost |
|---|---|---|---|---|---|
| 1:10 | 30 | 23.4 | $7 | $74.90 | $81.90 |
| 1:5 | 30 | 11.7 | $7 | $37.40 | $44.40 |
| 1:2 | 30 | 4.7 | $7 | $15.00 | $22.00 |
| 1:1 | 30 | 2.34 | $7 | $ 7.49 | $14.50 |
| 1:0.5 | 30 | 1.17 | $7 | $ 3.74 | $10.70 |

[1]The fair 1999 market value of HSA is approximately $3.20 per gram.

*Id.* at 34.

84.    Similar to the nanoparticle-based formulations of Desai, the albumin-
paclitaxel formulations of Kadima are "essentially free of toxic ingredients such as
Cremophor." *Id.* at 28.

## C.    Liversidge (EX1005)

85.    Liversidge issued on March 21, 1995, and is therefore prior art to the
'260 patent. EX1005.

86.    I was already familiar with Liversidge prior to my work in this pro-
ceeding, as I was a testifying expert for Elan Pharma International, which I under-
stand owns Liversidge, in litigation asserting Liversidge against the Patent Owner
in this proceeding. *Elan Pharma Int'l Ltd. v. Abraxis BioScience, Inc.*, C.A. No.

06-438-GMS (D. Del.). In that litigation, a jury determined that Liversidge was a valid patent, and that Patent Owner's product, Abraxane—an alleged embodiment of the '788 patent—infringed Liversidge. EX1011.

87. Liversidge generally discloses particle-based "anticancer compositions" comprising an "anticancer agent having a surface modifier adsorbed on the surface thereof in an amount sufficient to maintain an effective average particle size of less than about 1000 nm," and methods of administering such pharmaceutical compositions. EX1005, 1:49–65.

88. The "anticancer agent" of Liversidge may be paclitaxel (*id*. at 2:50, 3:20), and the "[p]articularly preferred surface modifiers" for the particles include albumin (*id*. at 4:23, 48).

89. Liversidge provides that, "[i]n particularly preferred embodiments of the invention, the effective average particle size is less than about 400 nm," and "[i]n some embodiments of the invention, the effective average particle size is less than about 300 nm." *Id*. at 5:1–5.

90. Liversidge teaches that the "[t]he surface modifier can be present in an amount of 0.1–90% … based on the total weight of the dry particle." *Id*. at 7:1–4. Consistent with that teaching, claim 1 of Liversidge is directed to "[p]articles consisting essentially of 99.9–10% by weight of a crystalline medicament useful in treating cancer" and a "surface modifier adsorbed on the surface thereof in an

amount of 0.1–90% by weight." *Id.* at 14:7–14, p. 10 (correcting 14:7)—*i.e.*, an albumin-paclitaxel ratio of 0.01:9.99 to 9:1.

91.    Liversidge also explains that "the particular anticancer agent surface modifier combination can be optimized" by skilled artisans employing routine methods, and describes a "simple screening process" for confirming that "[t]he resulting dispersion is stable." *Id.* at 7:5–46; *see id.* at 7:35–36.

## VI.    ANTICIPATION

92.    In my opinion, claims 1–9 and 11–12 are unpatentable as anticipated by WO 99/00113 to Desai et al. ("Desai") (EX1006), which discloses every limitation of each of these claims. I explain the bases for my opinion below.

### A.    Claims 1–9 and 11–12 of the '788 patent are anticipated.

#### 1.    Claim 1 is anticipated by Desai.

93.    Claim 1 of the '788 patent states as follows, with the bracketed letters added to delineate the claim's three limitations:  "**[a]** A pharmaceutical composition for injection comprising paclitaxel and a pharmaceutically acceptable carrier, wherein the pharmaceutically acceptable carrier comprises albumin, **[b]** wherein the albumin and the paclitaxel in the composition are formulated as particles, wherein the particles have a particle size of less than about 200 nm, and **[c]** wherein the weight ratio of albumin to paclitaxel in the composition is about 1:1 to about 9:1." In my opinion, each limitation of claim 1 is disclosed in and enabled by Desai, which therefore anticipates this claim.

### a.     Albumin-paclitaxel combination

94.     Example 1 of Desai discloses the combination of paclitaxel and albumin as a carrier. EX1006, 62. As Desai makes clear, these components are formulated as a pharmaceutical composition for injection. Example 1 states that "[t]he dispersion was further lyophilized," and "[t]he resulting cake could be easily reconstituted to the original dispersion by addition of sterile water or saline." *Id.* at 63. Desai explains that this lyophilization process "produces a sterile solid formulation useful for intravenous injection" (*id.* at 26), and that "a lyophilized powder" is useful "for reconstitution and intravenous administration." *Id.* at 28. Desai as a whole is also directed to "methods for the production of particulate vehicles for the intravenous administration of pharmacologically active agents." *Id.* at 3. Thus, Example 1 meets claim 1's requirement of "[a] pharmaceutical composition for injection comprising paclitaxel and a pharmaceutically acceptable carrier, wherein the pharmaceutically acceptable carrier comprises albumin."

### b.     Particle size of less than about 200 nm

95.     Example 1 of Desai also discloses that the albumin-paclitaxel formulation comprises nanoparticles having a typical average diameter of 160–220 nm, measured as the Z-average using a Malvern Zetasizer. *Id.* at 63. All of the average diameters within this typical range fall within the "about 200 nm" limit of claim 1, which, as I discussed above in paragraph 54, includes particles of 220 nm or less,

measured as the Z-average diameter using a Malvern Zetasizer. Example 1 thus necessarily produces a product that satisfies claim 1's "about 200 nm" limitation

96.    Moreover, I note that Desai's overall "preferred size range of the particles is between about 50 nm – 170 nm," which falls completely within the "about 200 nm" limit of claim 1. *Id.* at 54.

97.    Desai also "enables the reproducible production of unusually small nanoparticles of less than 200 nm diameter." *Id.* at 1; *id.* at 23 ("The invention further provides a method for the reproducible formation of unusually small nanoparticles (less than 200 nm diameter)."), 52 (describing a process "to obtain … particles <200 nm"), 54 (describing the production of "nanoparticles … in the range of about 10 nm – 200 nm diameter"). In my opinion, a skilled artisan would have agreed that the methods recited in Desai allowed for the formation of albumin-paclitaxel particles of less than about 200 nm.

98.    Thus, Example 1 of Desai meets claim 1's limitation requiring that "the albumin and the paclitaxel in the composition are formulated as particles, wherein the particles have a particle size of less than about 200 nm."

### c.    Albumin-paclitaxel ratio of about 1:1 to 9:1

99.    Example 1 of Desai further discloses a weight ratio of albumin to paclitaxel of about 9:1 by providing that "30 mg paclitaxel is dissolved in 3.0 ml methylene chloride," and further provides that "[t]he solution was added to 27.0 ml

of human serum albumin solution (1% w/v)." *Id.* at 62.

100. As a skilled artisan would have understood, 27 ml of 1% (w/v) albumin corresponds to 270 mg of albumin, and, when combined with 30 mg of paclitaxel, necessarily results in a composition with an albumin-paclitaxel weight ratio of 270:30, *i.e.*, exactly 9:1. As I discussed above in paragraphs 35–38 and 53, this method of calculating the ratio of albumin to paclitaxel based on the starting ingredients for making the composition is the same as the method of calculating the ratio in the examples of the '788 patent. Thus, Example 1 of Desai meets claim 1's limitation requiring that "the weight ratio of albumin to paclitaxel in the composition is about 1:1 to about 9:1." Accordingly, Desai discloses each limitation of claim 1 and therefore anticipates it.

**2. Claims 2–9 and 11–12 are anticipated by Desai.**

101. Claim 2 incorporates the limitations of claim 1 and requires the albumin to be human serum albumin, which is the albumin used in Example 1 of Desai. *Id.* at 62 ("The solution was added to 27.0 ml of human serum albumin solution …."). Thus, Desai also anticipates claim 2.

102. Claim 3 further requires that the composition is free of Cremophor, and no Cremophor is added to the composition of Example 1 of Desai. *Id.* at 62–63. For example, Desai discloses that a "cremophor-free formulation will be significantly less toxic" and that a "preferred embodiment" is "free of cremophor."

*Id.* at 27–28, 30. Thus, Desai anticipates claim 3.

103. Claim 4 covers a method of administering the composition of claim 1 to treat cancer, arthritis, or restenosis. Claims 5–7 depend from claim 4 and specify that the disease is cancer, arthritis, and restenosis, respectively. Desai's compositions in general are directed to treating these diseases. Indeed, the primary objective of Desai is to provide formulations of paclitaxel that are "significantly less toxic and more efficacious than Taxol®," in order to "increas[e] the efficacy of treatment of cancers." *Id.* at 4. Desai also "incorporate[s] by reference as if reproduced in full" numerous "patents, scientific articles, and other documents" evidencing the use of paclitaxel to treat the claimed diseases. *Id.* at 12–20.

104. Furthermore, Example 45 of Desai discloses a study and method of treating mammary tumors by administering an effective amount of albumin-paclitaxel nanoparticles, and concludes that "the intravenous administration of nanoparticles of paclitaxel can be as efficacious as administering the drug in the soluble form," *i.e.*, as efficacious as Taxol, which was FDA-approved to treat cancer before December 2002. *Id.* at 123, 7, 12. Moreover, claims 7, 15, 22, and 28 of Desai are directed to methods of using albumin-paclitaxel nanoparticles to treat tumors and/or cancer. *Id.* at 162–65.

105. Similarly, Example 46 discloses a study and method of treating rheumatoid arthritis, concluding that "the paclitaxel-containing nanoparticles demon-

strated therapeutic effect on arthritis." *Id*. at 124. Citing animal data in Figure 2, Desai concludes that albumin-paclitaxel nanoparticles showed "a dramatic reduction" in symptoms, "indicating a regression of arthritis." *Id*. at 35–36, 172.

106. Desai also explains that "applications of th[e] [claimed] formulation of paclitaxel includ[e] methods … for the treatment of restenosis." *Id*. at 30–31. Example 47 shows the use of albumin-paclitaxel nanoparticles "in inhibiting restenosis following intimal trauma of the artery." *Id*. at 125.

107. As a result, a skilled artisan would understand that Desai teaches methods of using albumin-paclitaxel nanoparticles to treat cancer, arthritis, and restenosis. Desai thus anticipates claims 4–7.

108. Claims 8 and 9 ultimately depend from claim 4 and require "intravenously" delivering the nanoparticle composition of claim 1. Desai as a whole concerns "the intravenous administration of pharmacologically active agents," and Example 1 states that "[t]he dispersion was further lyophilized," and "[t]he resulting cake could be easily reconstituted to the original dispersion by addition of sterile water or saline." *Id*. at 3, 63. As Desai explains, this "lyophilized powder" is designed "for reconstitution and intravenous administration." *Id*. at 28. Example 45 also discloses a study and method of treating mammary tumors using albumin-paclitaxel nanoparticles as a bolus intravenous injection. *Id*. at 122–23. Similarly, Example 52 discloses the intravenous delivery of albumin-paclitaxel nanoparticles.

*Id.* at 131–32. In addition, claims 6, 14, 21, and 27 of Desai are directed to methods of administering albumin-paclitaxel nanoparticles by routes including intravenous delivery. *Id.* at 162–64. Thus, Desai anticipates claims 8 and 9.

109.    Claim 11 depends from claim 1 and limits the albumin-paclitaxel ratio to 1:1 to 9:1, whereas claim 12 limits the albumin-paclitaxel ratio to about 9:1. As I discussed above, Example 1 of Desai discloses a composition with an albumin-paclitaxel ratio of 9:1 (*id.* at 62–63), and thus anticipates claims 11 and 12.

110.    Accordingly, Desai discloses every limitation of each of claims 1–9 and 11–12, and therefore anticipates each of these claims.

**B.    The "starting" ratio of albumin to paclitaxel does not change.**

111.    Petitioners' counsel has informed me that Patent Owner may argue that Example 1 of Desai does not disclose an albumin-paclitaxel ratio of about 9:1, because the "final" ratio obtained after following the steps of Example 1 will supposedly be higher than the "starting" ratio of the ingredients used to make the composition, due to the loss of paclitaxel during manufacturing. In support of that argument, I understand that Patent Owner may rely on Desai's disclosure that "Capxol™ is … produced by the method of Example 1," and "[e]ach vial of Capxol™ contains 30 mg of paclitaxel and approximately 400 mg of human serum albumin," which corresponds to an albumin-paclitaxel ratio of 13.3:1. EX1006, 38. I disagree with this argument, and a skilled artisan would disagree as well.

112. As I discussed above in paragraph 53, a skilled artisan would have understood that the "ratio" in the challenged claims includes at least the ratio of the starting ingredients used to make the composition. Indeed, as I explained above in paragraphs 35–38, every example in the '788 patent that mentions an albumin-paclitaxel ratio calculates this ratio based on the proportion of starting materials—not some materially different "final" ratio. This makes sense because formulators, similar to chefs, typically measure weight ratios of starting ingredients.

113. Moreover, a skilled artisan would not have expected the method of Example 1 of Desai to result in any loss of paclitaxel during manufacturing that would affect the albumin-paclitaxel ratio of the composition. There is no mention in Desai of any such loss of paclitaxel. And there is no reason why any of the steps of Example 1 of Desai would result in such a loss.

114. Although Desai states that Capxol contains albumin and paclitaxel in a 13.3:1 ratio, and states that Capxol is made according to the method of Example 1 (*id*. at 38), a skilled artisan would have understood that the reference to Capxol being made by the method of Example 1 simply refers to the general method of preparing "nanoparticles … by high pressure homogenization of a solution of USP human serum albumin and a solution of paclitaxel in an organic solvent." *Id*. at 39. Indeed, Example 1 is titled "Preparation of Nanoparticles by High Pressure Homogenization," and describes the homogenization of a solution of human serum al-

bumin and a solution of paclitaxel dissolved in methylene chloride. *Id.* at 62.

115. Thus, a skilled artisan would have understood that the method of Example 1 could be used to produce various embodiments of the albumin-paclitaxel nanoparticles disclosed in Desai, and was not limited to making Capxol. In other words, a skilled artisan would understand that Example 1 provides a method of making an albumin-paclitaxel composition *like* Capxol, but that does not necessarily result in Capxol.

116. Moreover, a skilled artisan would not have believed that Capxol, which contains 30 mg of paclitaxel and *400 mg* of albumin (corresponding to an albumin-paclitaxel ratio of 13.3:1), is made using the disclosed starting materials of Example 1, *i.e.*, 30 mg of paclitaxel and *270 mg* of albumin (corresponding to a ratio of 9:1). Nor would a skilled artisan have believed that the difference between the ratios of Capxol and Example 1 results from the loss of paclitaxel during the steps of Example 1. On the contrary, Capxol contains the same amount of paclitaxel that is used in the starting materials of Example 1. It is the amount of albumin that is different: Capxol contains 400 mg, whereas Example 1 uses only 270 mg. There is no step in Example 1 in which any additional albumin beyond the initial 270 mg is added, and thus a skilled artisan would not have believed that following the steps of Example 1 would produce a composition with 400 mg of albumin.

117. A skilled artisan also would have realized that Example 1 was not the precise method of making Capxol, which is sterile filtered and filled into vials containing 30 mg of paclitaxel, because Example 1 does not mention sterile filtration or vials. *Compare id.* at 38–39 *with* 62–63.

118. Instead, from reading Desai as a whole, a skilled artisan would have understood that the more specific process of making Capxol specifically (as opposed to the general process of making nanoparticles by high-pressure homogenization) is disclosed in Example 16, which recites Desai's "Presently Preferred Manufacturing Process." *Id.* at 75. As I discussed in paragraphs 68–70, Example 16 provides a method of producing a sterile-filtered composition with an albumin-paclitaxel ratio of 13.3:1, which is filled into vials containing 30 mg of paclitaxel.

119. Accordingly, Desai's disclosure that Capxol has a 13.3:1 ratio of albumin to paclitaxel and is made using the method of Example 1 does not change my opinion that Desai anticipates each of the challenged claims.

## VII. OBVIOUSNESS

120. It is also my opinion that all challenged claims of the '788 patent would have been obvious to a skilled artisan over Desai, either alone or in combination with Kadima (EX1004) and Liversidge (EX1005).

### A. Claim 1 of the '788 patent would have been obvious.

#### 1. Obviousness over Desai alone

121. As I noted above, claim 1 of the '788 patent claims the following,

with the bracketed letters added to delineate the claim's three primary limitations: "**[a]** A pharmaceutical composition for injection comprising paclitaxel and a pharmaceutically acceptable carrier, wherein the pharmaceutically acceptable carrier comprises albumin, **[b]** wherein the albumin and the paclitaxel in the composition are formulated as particles, wherein the particles have a particle size of less than about 200 nm, and **[c]** wherein the weight ratio of albumin to paclitaxel in the composition is about 1:1 to about 9:1." EX1001, 38:17–24.

122. In my opinion, to the extent there are any differences between Desai and claim 1 of the '788 patent (and, as discussed above, it is my opinion that there are no differences), any such differences would have been obvious to a skilled artisan as of December 2002 in view of Desai.

123. First, it would have been obvious to a skilled artisan in December 2002 to formulate paclitaxel and albumin as a pharmaceutical composition for injection. Indeed, Desai is primarily directed to such compositions. EX1006, 25. "The two major components of Capxol™"—the main focus of Desai—"are unmodified paclitaxel and human serum albumin (HSA)." *Id.* at 28. Moreover, the objective of Desai is to provide a "pharmaceutically acceptable formulation" (*id.* at 36), and Capxol is designed for "intravenous administration" (*id.* at 28, 38).

124. Second, it would have been obvious to a skilled artisan in December 2002 to formulate the paclitaxel and albumin as particles with a particle size of less

than 200 nm. Desai states that, "[i]n a preferred embodiment, the average diameter of the above-described particles is no greater than about 200 nm," because "[s]uch particles are particularly advantageous." *Id.* at 38. More specifically, Desai states that "[t]he preferred size range of the particles is between about 50 nm – 170 nm." *Id.* at 54.

125.    As Desai explains, "form[ing] nanoparticles of a size that is filterable by 0.22 micron filters"—*i.e.*, particles that will pass through a 220-nm filter, which is smaller than most microorganisms such as bacteria—"is of great importance and significance, since formulations which contain a significant amount of any protein (*e.g.*, albumin), cannot be sterilized by conventional methods" of removing bacteria from drugs by heating, "due to the heat coagulation of the protein." *Id.* at 24. Accordingly, Desai would have motivated a skilled artisan as of December 2002 to formulate paclitaxel and albumin as particles with a size less than 200 nm.[1]

---

[1] A skilled artisan would have known that regulatory guidelines issued by the FDA and its European counterpart before December 2002 similarly required nanoparticle drug products to have nanoparticles smaller than 220 nm in diameter in order to provide for sterile filtration. EX1009, 29–30 (1997 FDA Guideline: "Filtration is a common method of sterilizing drug product solutions…. Such filters usually have a rated porosity of 0.22 micron or smaller."); EX1010, 6 (1996

126. In so doing, a skilled artisan would have had a reasonable expectation of success. Indeed, Desai expressly "enables the reproducible production of unusually small nanoparticles of less than 200 nm diameter." *Id.* at 1; *see also* 23 ("The invention further provides a method for the reproducible formation of unusually small nanoparticles (less than 200 nm diameter)."); *id.* at 52 (describing a process "to obtain … particles <200nm"); *id.* at 54. Again, a skilled artisan in December 2002 would have agreed that the methods described in Desai enabled the production of albumin-paclitaxel nanoparticles smaller than 200 nm.

127. Third, in addition to making a pharmaceutical composition for injection made up of albumin-paclitaxel nanoparticles smaller than about 200 nm, it would have been obvious to a skilled artisan as of December 2002 to provide that "the weight ratio of albumin to paclitaxel in the composition is about 1:1 to about 9:1," for the following reasons.

### a. The albumin-paclitaxel ratio of about 9:1 falls within a range disclosed by Desai.

128. As an initial matter, Desai discloses a range of ratios of albumin to paclitaxel, and a ratio of about 9:1 is among the ratios within that range. As I discussed above in paragraphs 67 and 71, Example 1 of Desai discloses a 9:1 ratio,

---

EMEA Guideline: "For sterilisation by filtration," "sizes of 0.22 μm or less are acceptable").

and other examples in Desai disclose higher ratios, including 9.8:1, 12.9:1, and 13.3:1. Thus, the ratio of about 9:1 falls within a range disclosed in Desai.

129. Even assuming that Example 1 somehow does not expressly disclose a 9:1 ratio because the ratio would increase during manufacturing (an assumption with which I disagree, for the reasons I discussed above), an albumin-paclitaxel ratio of about 9:1 nevertheless falls within a range of ratios covered by Desai. Indeed, Desai specifically states that its examples are "non-limiting," and generally discloses a process for making albumin-paclitaxel nanoparticle formulations in which albumin "is added at a concentration in the range of about 0.05 to 25% (w/v), more preferably in the range of about 0.5% – 5% (w/v)." EX1006, 50. Thus, concentrations of albumin as low as 0.05% (w/v) are encompassed by Desai, and concentrations as low as 0.5% (w/v) are "preferred."

130. A skilled artisan would have understood that this preferred range could be applied to Desai's various "non-limiting" examples. As applied to the method of Example 1, a 0.5% (w/v) concentration of albumin, as opposed to the 1% (w/v) concentration used by way of example, would result in a composition with half as much albumin, *i.e.*, a ratio of only 4.5:1 albumin to paclitaxel. A ratio of about 9:1 falls between this lower ratio and the higher ratio of 13.3:1 disclosed for Capxol.

131. I understand that where, as here, there is a range disclosed in the prior

art, and the claimed invention falls within that range, the burden of production falls upon the patentee to come forward with evidence that (1) the prior art taught away from the claimed invention; (2) there were new and unexpected results relative to the prior art; or (3) there are other pertinent secondary considerations. I am not aware of any evidence that would allow Patent Owner here to meet this burden.

132. First, I understand that a prior art reference does not "teach away" from a claimed invention unless it criticizes, discredits, or otherwise discourages investigation into the invention claimed. Applying this standard, I am not aware of any prior art reference that teaches away from selecting an albumin-paclitaxel ratio of about 9:1 from the broader range disclosed in Desai.

133. Second, as I discuss below in Section VII.C, it is my opinion that the albumin-paclitaxel ratio of about 9:1 has not been demonstrated to produce any new and unexpected results relative to the prior art.

134. Third, I am not aware of any other pertinent secondary considerations that would suggest that a ratio of about 9:1 would be unobvious. Accordingly, it is my opinion that selecting a ratio of albumin to paclitaxel of about 9:1 would have been obvious to a skilled artisan as of December 2002 for this reason alone.

> **b. A skilled artisan would have been motivated to lower Capxol's 13.3:1 albumin-paclitaxel ratio.**

135. Even assuming that the prior art does not disclose a range that includes an albumin-paclitaxel ratio of about 9:1, or that selecting the ratio of about

9:1 from such a range (both assumptions with which I disagree), it is my opinion that it would have been obvious to a skilled artisan as of December 2002 to modify Capxol by reducing its albumin-paclitaxel ratio from 13.3:1, which is disclosed in Desai, to an albumin-paclitaxel ratio of about 9:1.

136. Desai explains that "[i]t is desirable to reduce the[] infusion volume[]" of parenteral formulations "by developing formulations of paclitaxel that are stable at higher concentrations so as to reduce the time of administration." EX1006, 21. According to Desai, "the delivery of high doses of the pharmacologically active agent in relatively small volumes…. minimizes patient discomfort at receiving large volumes of fluid and minimizes hospital stay." *Id.* at 54. A skilled artisan reading these disclosures as of December 2002 would have understood that delivering higher doses of paclitaxel in smaller volumes, and thereby minimizing patient discomfort and infusion times, could be accomplished simply by increasing the concentration of paclitaxel relative to the only other ingredient in the Capxol formulation, *i.e.*, albumin, resulting in a lower albumin-paclitaxel ratio.

137. Moreover, Desai teaches that "higher doses of paclitaxel result in a higher response rate." *Id.* at 19. Higher doses can be provided more efficiently by using higher concentrations of paclitaxel. As Desai notes, it has been "shown that higher doses of TAXOL up to 250 mg/m$^2$ produced greater responses (60%) than the 175 mg/m$^2$ dose (26%) currently approved for TAXOL." *Id.* at 20.

138. Based on these disclosures, a skilled artisan as of December 2002 would have appreciated that Capxol could likewise be improved to provide higher concentrations of paclitaxel by either increasing the amount of paclitaxel, reducing the amount of albumin, or both, which would thereby reduce the composition's ratio of albumin to paclitaxel. In fact, Desai suggests that it is desirable "to obtain a higher loading of drug into the crosslinked protein shell." *Id*. at 79. Desai thus expressly suggests increasing the concentration of paclitaxel in the composition by increasing the amount of paclitaxel per particle relative to the amount of albumin coating the particle, rather than merely increasing the concentration of the reconstituted composition overall without altering the ratio of albumin to paclitaxel.

139. Moreover, as a general principle, formulators always seek to maximize the amount of active drug in a formulation (here, paclitaxel) and to minimize the amount of excipients (here, albumin) that are not needed. Therefore, a skilled artisan would have been motivated to use a ratio of albumin to paclitaxel of about 9:1 instead of Capxol's ratio of 13.3:1, with a reasonable expectation of success in retaining Capxol's other beneficial properties. Because the only difference between Capxol and the composition of claim 1 of the '788 patent is the ratio of albumin to paclitaxel, it follows that claim 1 of the '788 patent would have been obvious in view of the prior art's disclosure of a motivation to modify Capxol by increasing its concentration of paclitaxel relative to albumin.

### c. A skilled artisan would have reasonably expected an albumin-paclitaxel ratio of 9:1 to retain stability.

140. It is also my opinion that, in preparing a formulation with an albumin-paclitaxel ratio of about 9:1, a skilled artisan as of December 2002 would have reasonably expected success in retaining the stability of the Capxol formulation, notwithstanding albumin's role in the formulation as a known stabilizer.

141. In my opinion, nothing in Desai suggests that the albumin-paclitaxel ratio of 13.3:1 in Capxol is critical to maintaining stability of the formulation. In fact, Example 1, as I discussed above, uses a 9:1 ratio, and other examples in Desai use similar ratios that are also lower than 13.3:1. In addition, Desai teaches that the concentration of albumin used in its "non-limiting" examples can be varied by the skilled artisan, and Desai encourages skilled artisans to "obtain a higher loading of drug into the crosslinked protein shell" (EX1006, 79). Desai never warns about any risks of destabilizing the formulation if the proportion of albumin to paclitaxel used in the formulation is somewhat less than 13.3:1. A skilled artisan in December 2002 would not have been concerned about such risks, either.

142. Although albumin is disclosed as a stabilizer, and a skilled artisan would have expected albumin to stabilize the composition, there is no reason why a skilled artisan would have expected a relatively minor reduction in the albumin-paclitaxel ratio from 13.3:1 to about 9:1 to have caused any problematic issue of physical instability.

143. Rather, Desai teaches simply that it is the presence of albumin on the surface of the particles, and albumin's inherent stabilizing properties, that provide stability to the formulation: "Since albumin is present on the colloidal drug particles (formed upon removal of the organic solvent), formation of a colloidal dispersion which is stable for prolonged periods is facilitated, due to a combination of electrical repulsion and steric stabilization." EX1006, 25. There is no suggestion in Desai that an albumin-paclitaxel ratio above about 9:1 is necessary to achieve this stabilizing effect. Nor is there any reason why so much albumin would be needed to form a crosslinked albumin shell around the paclitaxel particles. In fact, because a formulation with an albumin-paclitaxel ratio of about 9:1 would also have "albumin … present on the colloidal drug particles," including on the surface of the particles bound to paclitaxel, Desai expressly suggests that such a formulation would also have been expected to be "stable for prolonged periods." *Id.*

144. Moreover, Desai makes clear that Capxol has unusually exceptional stability, suggesting that less albumin could be used while maintaining a sufficiently stable formulation. Example 37 of Desai discloses that Capxol was reconstituted at concentrations as high as "15 mg/ml and stored at room temperature," and the "suspension[] was found to be homogeneous for at least three days" with "no change in [particle] size distribution" and "[n]o precipitation." EX1006, 116. Thus, even if reducing the albumin-paclitaxel ratio from 13.3:1 to about 9:1 could

be expected to cause some reduction in stability, a minor reduction in stability would not have dissuaded a skilled artisan from attempting that modification.

145. As Desai explains, Taxol, which was and remains a frequently used and commercially successful formulation, "precipitates in within about 24 hours after reconstitution at the recommended concentrations of 0.6–1.2 mg/ml." *Id.* Thus, a skilled artisan would have expected even a substantially less stable formulation than Capxol to be stable enough for therapeutic and commercial purposes.

146. In fact, a skilled artisan would have only needed the formulation to remain stable for long enough to infuse a therapeutic dose of the drug, and there is no question that such a short amount of time to maintain stability would have been expected. Indeed, articles by Damascelli et al. and Ibrahim et al. each reported that albumin-paclitaxel nanoparticles had been administered to human patients with a 30-minute infusion time, and neither reference reports any problems regarding stability during infusion. EX1017, Damascelli at 4, 10; EX1018, Ibrahim at 1 (each disclosing 30-minute infusions in clinical studies).

147. In any event, a skilled artisan would have been able to optimize the albumin-paclitaxel ratio by balancing the need for stability with the desirability of a higher drug concentration, and verify the typical parameters of stability using the same routine methods shown in Example 37 of Desai. EX1006, 116.

148. Accordingly, for at least these reasons, a skilled artisan as of Decem-

ber 2002 would have reasonably expected success in maintaining at least adequate, if not excellent, physical stability in reducing Capxol's albumin-paclitaxel ratio of 13.3:1 to about 9:1. The modification therefore would have been obvious.

### 2. Obviousness over Desai, Kadima, and Liversidge

149. Even if claim 1 of the '788 patent were not obvious over Desai alone, it would at least have been obvious to a skilled artisan over Desai in combination with Kadima and Liversidge, for the following reasons.

### a. Kadima and Liversidge also disclose ranges of albumin-paclitaxel ratios, including about 9:1.

150. Kadima discloses ratios of albumin to paclitaxel that include a ratio of about 9:1. Specifically, Kadima teaches that "[p]aclitaxel and albumin can be present" in its disclosed formulations "in a ratio of about 1:0.5 to about 1:10 (paclitaxel:albumin)," *i.e.*, an albumin-paclitaxel ratio of about 0.5:1 to about 10:1, which includes a ratio of about 9:1. EX1004, 32. Kadima recites selected ratios within this range from 0.5:1 to 10:1 in Kadima's table of expected costs for various formulations. *Id.* at 34. Other passages in Kadima likewise discuss "a ratio of about 1:0.5 to about 1:10" (paclitaxel-albumin ratio), and disclose data for ratios within that range. *Id.* at 41, 49–50.

151. While Kadima does not focus on nanoparticle-based formulations like Desai's, Kadima nevertheless would have informed a skilled artisan as of December 2002 that pharmaceutically acceptable albumin-paclitaxel formulations could

have lower albumin-paclitaxel ratios, and a skilled artisan would have been interested in exploring, with a reasonable expectation of success, such lower ratios in the context of Desai's nanoparticle-based formulations.

152. Indeed, Kadima's albumin-paclitaxel ratios are covered by Liversidge, which, as I discussed above, is directed to nanoparticle-based formulations that include Desai's and the '788 patent's formulations. *Id.*; EX1005. Specifically, Liversidge discloses and claims "[p]articles consisting essentially of 99.9–10% by weight" of an anticancer agent and "0.1–90% by weight" of a surface modifier, where the anticancer agent may be paclitaxel and the surface modifier may be albumin. *Id.* at 14:7–14, p. 10 (correcting 14:7), 14:25 (paclitaxel), 16:8 (albumin). The percentages disclosed and claimed in Liversidge correspond to a range of albumin-paclitaxel ratios of 0.01:9.99 to 9:1.

153. For the same reasons I discussed above in paragraphs 131–134, I am not aware of any evidence that would render the ratio of about 9:1, which falls within ranges disclosed in both Kadima and Liversidge (as well as Desai), nonobvious. Thus, it is my opinion that making albumin-paclitaxel nanoparticles with a particle size of less than about 200 nm and an albumin-paclitaxel ratio of about 9:1 would have been obvious to a skilled artisan as of December 2002.

> **b.** **Kadima teaches additional reasons to lower a 13.3:1 ratio of albumin to paclitaxel to about 9:1.**

154. Kadima also corroborates the motivations expressed in Desai for re-

ducing the albumin-paclitaxel ratio of Capxol from 13.3:1 to about 9:1, by explaining a method of adjusting "the ratio of paclitaxel or derivative thereof to albumin" in the composition as a means of achieving "the smallest volumes for administration or lyophilization/reconstitution, which enables more rapid administration, if desired." EX1004 at 12–13. As discussed above, Desai similarly teaches the desirability of reducing the infusion volume to provide more rapid administration, and therefore a skilled artisan would have had a reason to apply Kadima's method of adjusting the albumin-paclitaxel ratio to Desai's disclosure that Capxol has an albumin-paclitaxel ratio of 13.3:1.

155. Furthermore, Kadima shows that a skilled artisan in December 2002 also would have been motivated to reduce Capxol's albumin-paclitaxel ratio from 13.3:1 to about 9:1 in order to obtain a substantially more cost-effective and commercially viable formulation. As Kadima explains, "[a]lbumin is a cost-limiting component for use in drug stabilization," because "[a]lbumin is an expensive ingredient." EX1004, 10, 33. Reducing its use "as a bulk stabiliz[er]" therefore allows the production of pharmaceutical formulations that are relatively "inexpensive to prepare." Id. at 10. As I discussed above, Kadima illustrates this point with examples of cost differences for various ratios of albumin to paclitaxel, confirming that human serum albumin is much more expensive than paclitaxel. Id. at 34. Based on these cost differences, a skilled artisan would have been motivated to re-

duce the ratio of albumin to paclitaxel in Capxol in order to reduce costs of production.

156. Although Kadima does not focus on nanoparticle-based formulations such as Capxol, the motivations it discloses for lowering the albumin-paclitaxel ratio—*i.e.*, reducing infusion volumes, reducing administration times, and reducing costs—apply regardless of the type of formulation that is used, and specifically apply to the nanoparticle-based formulations of Desai, such as Capxol.

157. More specifically, a skilled artisan would have been motivated to apply the teachings of Kadima to Capxol while retaining Capxol's nanoparticle-based formulation. As Desai explains, "nanoparticles can provide a pre-programmed duration of action, ranging from days to weeks to months from a single injection," and were expected to "offer several profound advantages over conventionally administered medicaments, including automatic assured patient compliance with the dose regimen, as well as drug targeting to specific tissues or organs." EX1006, 4.

158. As Desai further explains, it was expected that "the delivery of biologics in the form of a particulate suspension allows targeting to organs such as the liver, lungs, spleen, lymphatic circulation, and the like...." *Id.* at 29. Moreover, as "a nanoparticle formulation," Capxol was expected to "concentrate[] in tissues such as the prostate, pancreas, testes, seminiferous tubules, bone, etc., ... at a significantly higher level than a nonparticulate formulation of paclitaxel." *Id.* at 29–

30. Desai thus suggests nanoparticle formulations "may be utilized to treat cancers of these tissues with a higher efficacy than" nonparticulate formulations. *Id.* at 30. Desai also notes that "[t]he literature suggests that particles in the low hundred nanometer size range preferentially partition into tumors through leaky blood vessels at the tumor site," and "[t]he colloidal particles of paclitaxel in the Capxol™ formulation may therefore show a preferential targeting effect." *Id.* at 34.

159. In addition, Desai teaches that a "colloidal system of pharmacologically active agent allows for the delivery of high doses of the pharmacologically active agent in relatively small volumes," which "minimizes patient discomfort at receiving large volumes of fluid and minimizes hospital stay." *Id.* at 54. In particular, Desai explains that its albumin-paclitaxel nanoparticle formulations allow the reconstituted solution for injection to be prepared at a paclitaxel concentration of up to "20 mg/ml," which "offers [a] substantial advantage … as it results in smaller infusion volumes." *Id.* at 32.

160. Accordingly, for all of these reasons, a skilled artisan applying Kadima's teachings to modify the albumin-paclitaxel ratio of Capxol would otherwise have retained its nanoparticle-based formulation.

161. For these reasons, claim 1 of the '788 patent would have been obvious to a skilled artisan as of December 2002 over Desai, either alone or, at a minimum, in combination with Kadima and Liversidge.

**B.      The other challenged claims would have been obvious.**

162.   It is my opinion that the remaining challenged claims of the '788 patent also would have been obvious over Desai, either alone or in combination with Kadima and Liversidge. I explain the basis for my opinion as follows.

163.   As I noted above in paragraph 101 regarding anticipation, claim 2 of the '788 patent incorporates the limitations of claim 1 and further specifies that the albumin used is human serum albumin. Desai renders this limitation obvious because human serum albumin is the albumin recited and exemplified repeatedly throughout Desai, including as the type of albumin used for Capxol. *E.g.*, EX1006, 28. Moreover, it would have been obvious to use human albumin, as opposed to other types of albumin, in a pharmaceutical composition designed for administration to humans. Thus, claim 2 would have been obvious.

164.   Claim 3 of the '788 patent incorporates the limitations of claim 1 and further requires that the composition is free of Cremophor.  Desai renders this limitation obvious by teaching that Capxol is "a cremophor-free formulation," and by predicting "based on animal studies … that a cremophor-free formulation will be significantly less toxic and will not require premedication of patients," which would otherwise be "necessary to reduce the hypersensitivity and anaphylaxis that occurs as a result of cremophor." *Id*. at 27–28. Thus, claim 3 of the '788 patent would have been obvious to a skilled artisan.

165. Claim 4 is directed to a method of treating cancer, arthritis, or restenosis by administering the composition of claim 1, and claims 5–7 narrow claim 4 to require that the disease is cancer, arthritis, and restenosis, respectively. As Desai acknowledges, paclitaxel was known and approved in the United States to treat cancer in humans. *Id.* at 7, 12. Moreover, Example 45 discloses the treatment of mammary tumors using albumin-paclitaxel nanoparticles, and claims 7, 15, 22, and 28 are directed to methods of using Desai's disclosed compositions to treat a tumor and/or cancer. *Id.* at 122–23, 162–65. Similarly, Examples 46 and 47 are directed to the use of albumin-paclitaxel nanoparticles to treat rheumatoid arthritis and artery restenosis, respectively. *Id.* at 123–27. Thus, it would have been obvious to use the albumin-paclitaxel compositions covered by Desai—including a modified version of Capxol with a ratio of albumin to paclitaxel of about 9:1—to treat cancer, arthritis, and restenosis. Claims 4–7 thus would have been obvious.

166. Claim 8 incorporates the limitations of claim 4 and specifies that the composition is administered according to one of several listed delivery methods, including intravenous delivery. Claim 9 limits the delivery method of claim 8 to intravenous delivery. It would have been obvious to a skilled artisan to administer the composition of claim 1 intravenously in view of Desai, which is specifically directed to "the intravenous administration of pharmacologically active agents." *Id.* at 3. As Desai explains, "[i]ntravenous drug delivery permits rapid and direct equi-

libration with the blood stream which carries the medication to the rest of the body." *Id.* at 4. Moreover, Capxol is specifically designed for "intravenous administration" (*id.* at 28, 38); Examples 45 and 52 exemplify intravenous delivery of albumin-paclitaxel nanoparticles (*id.* at 122–23, 131–32); and claims 6, 14, 21, and 27 are directed to methods of administering Desai's disclosed compositions by routes including intravenous delivery (*id.* at 162–64). Thus, claims 8 and 9 of the '788 patent would have been obvious to a skilled artisan.

167.  Claim 10 incorporates the limitations of claim 1 and limits the albumin-paclitaxel ratio to about 1:1 to about 5:1.  For the same reasons discussed above in connection with claim 1, it would have been obvious over Desai, either alone or in combination of Kadima and Liversidge, to reduce Capxol™'s albumin-paclitaxel ratio of 13.3:1 to about 5:1 in order to increase the concentration of paclitaxel and/or reduce the cost of albumin.  Moreover, as discussed above, Liversidge and Kadima each cover ranges of albumin-paclitaxel ratios that include claim 10's range of about 1:1 to about 5:1.  Thus, for the same reasons discussed above in connection with claim 1, claim 10 would have been obvious.

168.  Claim 11 incorporates the limitations of claim 1 and limits the ratio of albumin to paclitaxel to 1:1 to 9:1.  Claim 12 further limits the ratio to about 9:1. As discussed in the preceding sections, it would have been obvious to make a composition that meets the limitations of claim 1 with a ratio of albumin to paclitaxel

of about 9:1 in view of Desai, either alone or in combination with Kadima and Liversidge. Thus, claims 11 and 12 would have been obvious to a skilled artisan as of December 2002.

**C.     There are no relevant secondary considerations indicating that the challenged claims would not have been obvious.**

169.     I am not aware of any evidence of secondary considerations that would tend to suggest that the challenged claims would have been unobvious.

170.     However, I understand that the applicants for the '788 patent argued to the Patent Office that the secondary consideration of "unexpected results" supports the nonobviousness of the claims.  Specifically, I have reviewed a declaration by one of the named inventors, Neil P. Desai, which was submitted to the Patent Office as evidence that the albumin-paclitaxel ratio of about 9:1 would not have been obvious. EX1023 (the "Inventor Declaration").

171.     The Inventor Declaration alleges the discovery of "unexpected results associated with the claimed albumin/paclitaxel ratio, including striking biological and clinical data relating to the ratio." *Id*. ¶ 6. The Declaration claims that the applicants "found, unexpectedly, that the ratio of albumin to paclitaxel in an albumin based paclitaxel nanoparticle composition affects the ability of paclitaxel to bind to endothelial cells," and that "the effect of albumin/paclitaxel ratio on the binding of paclitaxel changes dramatically at an albumin/paclitaxel ratio of about 9:1." *Id*. ¶ 7. The Declaration further claims that the applicants "found unexpectedly that

Abraxane®, an albumin-based paclitaxel nanoparticle composition having about 9:1 albumin/paclitaxel weight ratio, is more efficacious than [an] old formulation (about 19:1 albumin/paclitaxel ratio) in treating cancer" (called "ABI-007"), and that the applicants "further unexpectedly found that Abraxane® has substantially reduced toxicity compared with the old formulation." *Id.* ¶ 23.

172. After reviewing the Inventor Declaration and its exhibits, my opinion is that they do not demonstrate any relevant unexpected results regarding the claims of the '788 patent. I explain the bases for my opinion below.

### 1. The allegedly "unexpected" cell-binding results lack a nexus to the '788 patent and would have been expected.

173. I have been informed that a connection or "nexus' must be identified between the alleged unexpected results and the claimed subject matter in order to provide evidence that an alleged invention would not have been obvious. In my opinion, the "cellular binding" results disclosed in the Inventor Declaration lack such a nexus to the challenged claims, for at least two reasons.

174. First, in performing the "cell-binding" experiment in the Inventor Declaration, the applicants did not test the claimed combination of albumin and paclitaxel. Instead, they tested a *different* combination of albumin and "[*f*]luorescent paclitaxel" (EX1023 ¶¶ 9–11)—*i.e.*, a fluorescein-paclitaxel conjugate. As the '788 patent shows, the fluorescein-paclitaxel conjugate that the applicants tested, and which I understand was commercially available at the time, is sold un-

der the name Flutax. *See* EX1001, 33:24–34:67 (Examples 40–44, describing the use of "Flutax" in albumin-binding experiments).

175. Importantly, a skilled artisan would have expected Flutax to have a different molecular weight, different solubility, and different protein-binding properties than paclitaxel alone. In particular, fluorescein was also known to bind to human serum albumin. EX1007. As a result, a skilled artisan would not have drawn conclusions about the cell-binding properties of the combination of paclitaxel and albumin from results obtained with the combination of Flutax and albumin, because the results could have been driven or largely affected by the binding of the fluorescein moiety of Flutax rather than its paclitaxel moiety. Accordingly, the results in the Inventor Declaration lack an adequate nexus to the combination of albumin and paclitaxel claimed in the '788 patent.

176. Second, the asserted results also lack a nexus to the claims of the '788 patent because the inventors did not test the claimed albumin-paclitaxel ratio of "about 9:1." Rather, as stated in the Declaration, they tested ratios "*above* about 9:1" and "about 9:1 *or less*." EX1023 ¶ 14. This is confirmed by the chart in Exhibit 4 to the Inventor Declaration, depicted below, which shows that the tested compositions were *outside* the labeled "[r]egion of ratio about 9:1":
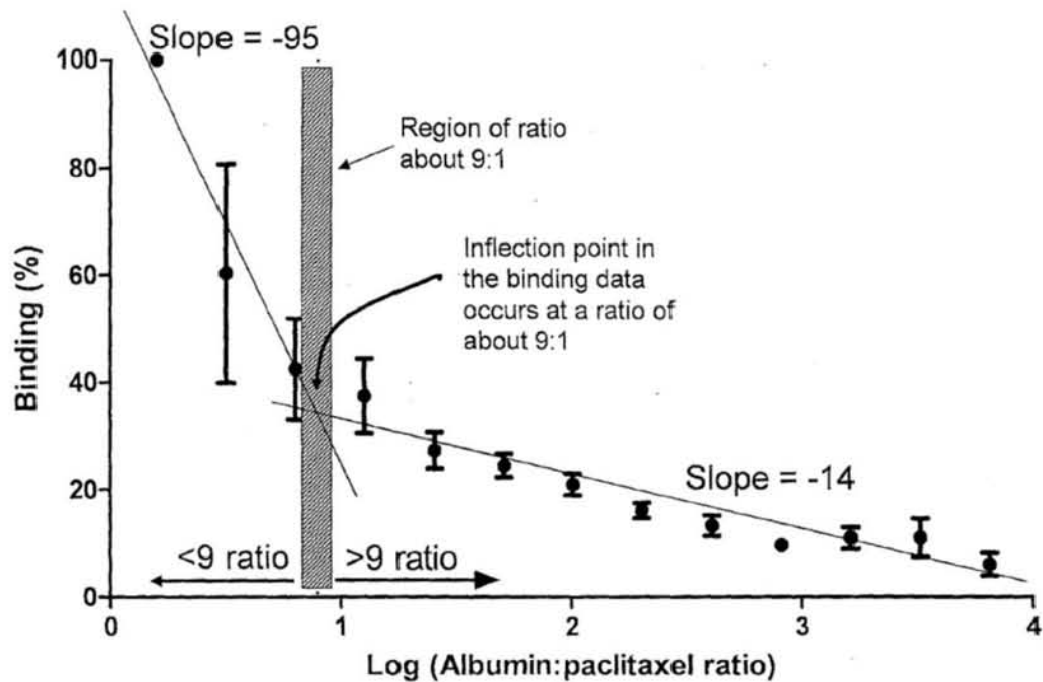
*Id.* at 19, Ex. 4. Thus, the test results disclosed in the Inventor Declaration do not have an adequate nexus to the claimed ratio of "about 9:1."

177. Even putting aside these nexus problems, a skilled artisan would not have drawn any conclusions from the data depicted above, as the statistical significance of the data was not reported. Citing the above chart (Exhibit 4), the Inventor Declaration states that "the effect of the albumin/paclitaxel ratio on the binding of paclitaxel changes dramatically at an albumin/paclitaxel weight ratio of about 9:1." *Id.* ¶ 14. Yet, given the large, overlapping error bars for the key data points, there is no evidence presented in the Inventor Declaration of any actual "inflection" point, and no disclosed scientific basis for extrapolating trends across the data.

178. In any event, a skilled artisan would have expected the results of the

experiment. The Inventor Declaration asserts that it would have been unexpected that "[h]igher albumin/paclitaxel ratios are associated with poor cellular binding of paclitaxel, while lower albumin/paclitaxel ratios are associated with enhanced cellular binding of paclitaxel." *Id.* ¶ 7. To a skilled artisan, however, that result would have been entirely expected from the experiment's design.

179.   In the experiment, "a hydrophobic surface coated with albumin" was "used to simulate a cellular membrane in a milieu of albumin." *Id.* ¶ 11. Naturally, as the amount of albumin was increased in the formulation (thereby increasing the albumin-paclitaxel ratio), a greater proportion of paclitaxel binded to the albumin in solution, which in turn reduced the amount of paclitaxel that was left available to bind to the hydrophobic surface. That is exactly what a skilled artisan would have expected. The results thus do not suggest any unexpected or even relevant relationship between "cellular binding" and the claimed invention.

180.   For all of these reasons, the asserted "unexpected" results related to cellular binding in the Inventor Declaration do not change my opinion that the challenged claims of the '788 patent would have been obvious to a skilled artisan.

### 2. The allegedly "unexpected" clinical data did not compare the closest prior art and would have been expected.

181.   I have been informed that when unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared to the closest prior art. In my opinion, the clinical results disclosed in the Inventor

Declaration and alleged to be "unexpected" fail to meet this requirement because they do not compare the claimed ratio of about 9:1 to the closest prior art ratio.

182.    The clinical data discussed in the Inventor Declaration compared Abraxane, which allegedly has an albumin-paclitaxel ratio of about 9:1, with "an old formulation developed by Abraxis" referred to by the internal code name "ABI-007." EX1023 ¶¶ 23, 17. As the Inventor Declaration states, "[t]he albumin/paclitaxel weight ratio in the old formulation was about 19:1." *Id.* ¶ 17.

183.    However, the "old formulation" with an albumin-paclitaxel ratio of 19:1 is not the closest prior art to the claimed formulation with a ratio of about 9:1. Rather, Example 1 of Desai is the closest prior art because, as I discussed above, it discloses a composition with a 9:1 ratio of albumin to paclitaxel. Moreover, as I discussed in paragraph 71, other examples in Desai disclose other ratios that are closer to 9:1 than 19:1, including ratios of 9.8:1 and 12.9:1.

184.    Even aside from these examples, Desai's disclosure of Capxol is closer prior art than the "old formulation" discussed in the Inventor Declaration, because Capxol has an albumin-paclitaxel ratio of 13.3:1, which is closer to the claimed ratio of about 9:1 than a ratio of 19:1. *See* EX1006, 38–39. Yet, the Inventor Declaration only compares Abraxane to the "old formulation" with a 19:1 ratio. EX1023 ¶¶ 23–30. It does not compare Abraxane to Capxol. Because the Inventor Declaration does not compare the claimed ratio to the closest prior art, it

does not show that the claimed ratio is unobvious.

185. For other reasons, moreover, a skilled artisan would not have drawn any conclusions from the clinical tests referenced in the Inventor Declaration. The declaration refers to "[t]wo clinical studies using Abraxane® ('the 9:1 formulation') and the old formulation ('the 19:1 formulation') [that] were conducted in China with cancer patients having various solid tumors," and compares the tumor shrinkage results observed across these two separate studies. *Id.* ¶¶ 25–27. However, no data, testing protocols, or related publications are included or cited in the Inventor Declaration regarding the tumor shrinkage results. Nor is there any way of knowing whether the separate tests on the two different formulations were conducted under the same or similar conditions.

186. The Declaration also states that adverse events were recorded during these two studies, and a table in Exhibit 5 to the Declaration, depicted below, purports to show a lower rate of adverse events in patients taking Abraxane than in patients taking the 19:1 formulation. *Id.* ¶ 28.

**Treatment-related Adverse Events of All Grades by NCI CTCAE Term**

| NCI CTCAE Term (Reported Adverse Event) | 9:1 formulation 260 mg/m² q3 Weeks (n=104) | 19:1 formulation 135-350 mg/m² (mean dose about 250 mg/m2) q3 Weeks (n=22) |
|---|---|---|
| Neurology: Neuropathy: Sensory | 79 (76%) | 19 (86%) |
| Blood/Bone Marrow: Lymphopenia | 6 (6%) | 8 (36%) |
| Blood/Bone Marrow: Leukocytopenia | 67 (64%) | 18 (82%) |
| Blood/Bone Marrow: Hemoglobinemia | 16 (15%) | 17 (77%) |
| Blood/Bone Marrow: Neutropenia | 72 (69%) | 14 (64%) |
| Pain: Myalgia | 40 (38%) | 10 (45%) |
| Pain: Arthralgia | 23 (22%) | 6 (27%) |
| Gastrointestinal: Anorexia | 19 (18%) | 16 (73%) |
| Gastrointestinal: Diarrhea | 16 (15%) | 5 (23%) |
| Gastrointestinal: Nausea | 24 (23%) | 8 (36%) |
| Dermatology/Skin: Rash/Desquamation | 27 (26%) | 9 (41%) |
| Dermatology/Skin: Pruritus/Itching | 22 (21%) | 5 (23%) |
| Constitutional Symptoms: Fatigue | 16 (15%) | 8 (36%) |

*Id.* at 21 (EX5).

187. This table reveals several problems. First, the patient group receiving the 19:1 ratio was small (n=22), especially compared to the much larger group receiving Abraxane (n=104), and no statistical significance was reported.

188. Second, the patients in the two groups did not receive the same doses. The patients taking Abraxane all received 260 mg/m², whereas patients in the 19:1 group received a range of doses from 135–350 mg/m². Although the mean dose was 250 mg/m², there is no median disclosed. Thus, a majority of patients in the

19:1 group could have taken substantially higher doses, which could have had a significant effect on the rate of adverse events. As demonstrated in Tables 1 and 4 of Ibrahim, it was known that adverse events in the old formulation increased dramatically at doses of 300 mg/m$^2$ and higher:

*Table 1   Dose levels*

| Level | Dose (mg/m$^2$) | No. patients entered | No. cycles |
|---|---|---|---|
| 0 | 135 | 4 | 6 |
| 1 | 200 | 3 | 38 |
| 2 | 300 | 6 | 35 |
| 3 | 375 | 6 | 17 |

*Table 4   Nonhematologic toxicity by dose level[a]*

| | Level 0 (n = 4) | | Level 1 (n = 3) | | Level 2 (n = 6) | | Level 3 (n = 6) | |
|---|---|---|---|---|---|---|---|---|
| Toxicity | Grade 1 or 2 | Grade 3 | Grade 1 or 2 | Grade 3 | Grade 1 or 2 | Grade 3 | Grade 1 or 2 | Grade 3 |
| Sensory neuropathy | 0 | 0 | 0 | 0 | 4 | 1 | 3 | 3 |
| Ocular | 1 | 0 | 0 | 0 | 2 | 0 | 2 | 2 |
| Stomatitis | 0 | 0 | 1 | 0 | 4 | 0 | 3 | 2 |
| Nausea | 1 | 0 | 1 | 0 | 3 | 0 | 4 | 1 |
| Vomiting | 1 | 0 | 1 | 0 | 0 | 0 | 2 | 1 |
| Diarrhea | 1 | 0 | 2 | 0 | 3 | 0 | 1 | 1 |
| Arthralgia/myalgia | 3 | 0 | 3 | 0 | 4 | 0 | 4 | 1 |
| Skin | 0 | 0 | 0 | 0 | 5 | 0 | 2 | 0 |
| Fever (non-neutropenic) | 0 | 0 | 0 | 0 | 2 | 0 | 3 | 0 |

[a] Expressed as the number of patients experiencing the toxic effect during the first two cycles of treatment.

EX1018, 2, 4. In Exhibit 5 of the Inventor Declaration, doses of 300 mg/m$^2$ were administered only to the 19:1 group, whereas all doses in the 9:1 group were below that threshold. EX1023, 21. Given this difference, in view of Ibrahim, a skilled artisan would have expected more adverse events in the 19:1 group.

189.   Third, critical details about the patient populations and treatment methods that could affect the results (both with respect to tumor shrinkage and adverse events) are not disclosed in the Inventor Declaration—*e.g.*, the drug infusion rates and the stage of cancer being treated.

190. Furthermore, I have been informed that to qualify as an "unexpected result," the result must be a difference in kind rather than a mere difference in degree. Here, the alleged unexpected results were not differences in kind, *i.e.*, a differences in the kind of effect that the formulations had on patients. Instead, Abraxane and the older formulation with an albumin-paclitaxel ratio of 19:1 had the same kinds of effects, but simply to a different degree.

191. For all of these reasons, the asserted "unexpected" results related to clinical effects in the Inventor Declaration do not change my opinion that the challenged claims of the '788 patent would have been obvious to a skilled artisan.

## VIII. CONCLUSION

192. In sum, for the reasons I have discussed above, it is my opinion that claims 1–12 of the '788 patent are anticipated by Desai (EX1006), and that claims 1–9 and 11–12 would have been obvious over Desai, either alone or in view of Kadima (EX1004) and Liversidge (EX1005).

193. I understand that this declaration will be filed as evidence in a contested case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I also understand that I may be subject to cross-examination concerning this declaration, and I will appear for cross-examination, if required of me, during the time allotted for cross-examination.

194. I hereby declare that all of the statements made herein are true of my

own knowledge and that all statements made on information and belief are believed to be true; and further that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Dated: November 8, 2017

_____
Cory J. Berkland, Ph.D.

# APPENDIX

**Cory J Berkland**
Solon E. Summerfield Distinguished Professor
Department of Chemical and Petroleum Engineering
Department of Pharmaceutical Chemistry
The University of Kansas

Office: (785)-864-1455
Multidisciplinary Research Building
2030 Becker Drive
Lawrence, KS 66047
berkland@ku.edu

## Education and Professional Training

| | |
|---|---|
| Sabbatical, Sofinnova Ventures, Menlo Park, CA | 2014 |
| Ph.D. Chemical and Biomolecular Engineering, University of Illinois, Urbana, IL | May 2003 |
| M.S. Chemical Engineering, University of Illinois, Urbana, IL | May 2001 |
| B.S. Chemical Engineering, Iowa State University, Ames, IA | December 1998 |

## Awards

| | |
|---|---|
| Bellows Scholar, The University of Kansas, Lawrence, KS | 2016 |
| Fellow of the American Institute of Medical and Biological Engineering | 2015 |
| Bellows Scholar, The University of Kansas, Lawrence, KS | 2014 |
| Jim Baxendale Commercialization Award, The University of Kansas, Lawrence, KS | 2014 |
| Iowa State University Professional Progress in Engineering Award, Ames, IA | 2013 |
| Leading Light Award, The University of Kansas, Lawrence, KS | 2013 |
| Miller Scholar, The University of Kansas, Lawrence, KS | 2013 |
| Controlled Release Society Young Investigator Award, Quebec City, Canada | 2012 |
| Coulter Foundation Fellow, The Coulter Foundation | 2012 |
| University Scholarly Achievement Award, The University of Kansas, Lawrence, KS | 2012 |
| Nagai Foundation Distinguished Lectureship, Annual DDS Conference, Shizuoka, Japan | 2011 |
| Miller Scholar, The University of Kansas, Lawrence, KS | 2011 |
| Kemper Fellowship for Teaching Excellence, The University of Kansas, Lawrence, KS | 2010 |
| Featured in Science Magazine Online, "The Entrepreneurial Bug" | 2009 |
| Bellows Scholar, The University of Kansas, Lawrence, KS | 2008 |
| Coulter Translational Research Award, The Coulter Foundation | 2008 |
| Teaching Achievement Recognition, Center for Teaching Excellence, Lawrence, KS | 2007 |
| Outstanding Reviewer for the Journal of Pharmaceutical Sciences | 2007 |
| Miller Scholar, The University of Kansas, Lawrence, KS | 2006 |
| Outstanding Reviewer for the Journal of Pharmaceutical Sciences | 2005 |
| Genencor Outstanding Paper Award, Controlled Release Society, Honolulu, HI | 2004 |
| Best Presentation, Chemical and Biomolecular Engineering Symposium, Urbana, IL | 2003 |
| Graduate College Travel Award, Urbana, IL | 2003 |
| Highlights of Student Posters Award, Controlled Release Society, Seoul, Korea | 2002 |
| Whitaker Award, American Chemical Society, Particles meeting, Orlando, FL | 2002 |
| Featured Technology, University of Illinois Technology Showcase, Urbana, IL | 2001 |

## Publications

1.    Townsend JM, Dennis SC, Whitlow J, Feng Y, Wang J, Andrews B, Nudo RJ, Detamore MS, Berkland C (2017) Colloidal Gels with Extracellular Matrix Particles and Growth Factors for Bone Regeneration in Critical Size Rat Calvarial Defects., AAPS *in press*

2.    S Tima, S Anuchapreeda, C Ampasavate, C Berkland, S Okonogi, and (2017) Stable curcumin-loaded polymeric micellar formulation for enhancing cellular uptake and cytotoxicity to FLT3 overexpressing EoL-1 leukemic cells., European Journal of Pharmaceutics and Biopharmaceutics, *in press*

3.    Dennis SC, Whitlow J, Detamore MS, Kieweg SL, Berkland C (2017) Hyaluronic-Acid-Hydroxyapatite Colloidal Gels Combined with Micronized Native ECM as Potential Bone Defect Fillers, Langmuir, 33(1):206-218

4.    Ishiguro S, Alhakamy N, Uppalapati D, Delzeit J, Berkland C, Tamura M (2017) Combined local pulmonary and systemic delivery of AT2R gene by modified TAT peptide nanoparticles attenuates both murine and human lung carcinoma xenografts in mice, Journal of Pharmaceutical Sciences, 106(1):385-394

5.    Northrup L, Sullivan BP, Hartwell BL, Garza A, Berkland C (2017) Screening Immunomodulators To Skew the Antigen-Specific Autoimmune Response, Molecular Pharmaceutics, 14(1):66-80

6.    Teresk MG, Berkland CJ, Dormer NH (2017) Deficiencies in Traditional Oral Dosage Forms and the Emergence of Controlled-Release Powder Manufacturing, KONA: Powder and Particle Journal, 34:91-105

7.    Mohammadi Z, Sun S, Berkland C, Liang JT (2016) Chelator-mimetic multi-functionalized hydrogel: Highly efficient and reusable sorbent for Cd, Pb, and As removal from waste water, Chemical Engineering Journal 307:496-502

8.    S Tima, S Okonogi, C Ampasavate, C Pickens, C Berkland, and S Anuchapreeda (2016) Development and Characterization of FLT3-Specific Curcumin-Loaded Polymeric Micelles as a Drug Delivery System for Treating FLT3-Overexpressing Leukemic Cells., 105(12):3645-3657

9.    Berkland C, Middaugh CR (2016) Overcoming formulation challenges for the next generation of vaccines, Expert Opinion on Drug Delivery, 13(11):1501-1502

10.   Ruiz S, Bowen L, Berkland C, Bailey MM (2016) Formulation and Characterization of Nanocluster Ceftazidime for the Treatment of Acute Pulmonary Melioidosis, Journal of Pharmaceutical Sciences, 105(11):3399-3408

11.   Gupta V, Tenny KM, Barragan M, Berkland CJ, Detamore MS (2016) Microsphere-based scaffolds encapsulating chondroitin sulfate or decellularized cartilage, Journal of Biomaterial Applications, 31(3):328-343

12.   Fang WB, Yao M, Brummer G, Acevedo D, Alhakamy N, Berkland C, Cheng N (2016) Targeted gene silencing of CCL2 inhibits triple negative breast cancer progression by blocking cancer stem cell renewal and M2 macrophage recruitment, Oncotarget, 7(31):49349-49367

13.   Gupta V, Lyne DV, Barragan M, Berkland CJ, Detamore MS (2016) Microsphere-based scaffolds encapsulating tricalcium phosphate and hydroxyapatite for bone regeneration, Journal of Materials Science: Materials in Medicine, 27(7):121

14.   Kuehl C, Zhang T, Kaminskas LM, Porter CJ, Davies NM, Forrest L, Berkland C (2016) Hyaluronic Acid Molecular Weight Determines Lung Clearance and Biodistribution after Instillation, Molecular Pharmaceutics, 13(6):1904-14

15.   Sridharan B, Mohan N, Berkland CJ, Detamore MS (2016) Material characterization of microsphere-based scaffolds with encapsulated raw materials, Material Science and Engineering C: Materials for Biological Applications, 63:422-8

16.   Beck EC, Barragan M, Libeer TB, Kieweg SL, Converse GL, Hopkins RA, Berkland CJ, Detamore MS (2016) Chondroinduction from Naturally Derived Cartilage Matrix: A Comparison Between Devitalized and Decellularized Cartilage Encapsulated in Hydrogel Pastes, Tissue Engineering Part A, 22(7-8):665-679

17. Antunez LR, Livingston A, Berkland C, Dhar P (2016) Physiochemical properties of aluminum adjuvants elicit differing reorganization of phospholipid domains in model membranes, Molecular Pharmaceutics, 13(5):1731-7

18. Hartwell BL, Martinez-Becerra F, Chen J, Shinogle HE, Sarnowski M, Moore DS, Berkland C. (2016) Antigen-Specific Binding of Multivalent Soluble Antigen Arrays Induces Receptor Clustering and Impedes B Cell Receptor Mediated Signaling, Biomacromolecules, 17(3):710-22

19. Alhakamy NA, Dhar P, Berkland CJ (2016) Charge Type, Charge Spacing, and Hydrophobicity of Arginine-Rich Cell-Penetrating Peptides Dictate Gene Transfection., Molecular Pharmaceutics, 13(3):1047-57

20. Alhakamy NA, Ishiguro S, Uppalapati D, Berkland CJ, Tamura M (2016) AT2R Gene Delivered by Condensed Polylysine Complexes Attenuates Lewis Lung Carcinoma after Intravenous Injection or Intratracheal Spray, Molecular Cancer Therapeutics, 15(1):209-18

21. Hartwell BL, Smalter Hall A, Swafford D, Sullivan BP, Garza A, Sestak JO, Northrup L, Berkland C. (2015) Molecular Dynamics of Multivalent Soluble Antigen Arrays Support Two-Signal Codelivery Mechanism in Treatment of Experimental Autoimmune Encephalomyelitis, Molecular Pharmaceutics, 13(2):330-343

22. Northrup L, Christopher MA, Sullivan BP, Berkland C. (2016) Combining Antigen and Immunomodulators: Emerging Trends in Antigen-Specific Immunotherapy for Autoimmunity, Advanced Drug Delivery Reviews, 98:86-98

23. J Qian, BP Sullivan, and C Berkland (2015) pH-responsive micelle sequestrant polymers inhibit fat absorption, Biomacromolecules, 16(8):2340-2346

24. Gupta V, Mohan N, Berkland CJ, Detamore MS (2015) Microsphere-Based Scaffolds Carrying Opposing Gradients of Chondroitin Sulfate and Tricalcium Phosphate, Frontiers of Bioengineering and Biotechnology, 3:96

25. Mohan N, Gupta V, Sridharan B, Mellott AJ, Easley JT, Palmer RH, Galbraith RA, Key VH, Berkland CJ, Detamore MS, (2015) Microsphere-based gradient implants for osteochondral regeneration: a long term study in sheep, Regenerative Medicine, 10(6):709-728

26. Sutherland AJ, Beck EC, Dennis SC, Converse GL, Hopkins RA, Berkland CJ, Detamore MS. (2015) Decellularized cartilage may be a chondroinductive material for osteochondral tissue engineering, PLoS One, 10(5)

27. Sullivan BP, El-Gendy N, Kuehl C, Berkland C. (2015) Pulmonary Delivery of Vancomycin Dry Powder Aerosol to Intubated Rabbits, Molecular Pharmaceutics, 12(8):2665-2674

28. El-Gendy N, Qian J, Eshelman K, Rivera M, Berkland C. (2015) Antibiotic activity of iron-sequestering polymers, Biomacromolecules, 16(5):1480-1488

29. Alhakamy NA, Elandaloussi I, Ghazvini S, Berkland CJ, Dhar P. (2015) Effect of lipid headgroup charge and pH on the stability and membrane insertion potential of calcium condensed gene complexes, Langmuir, 31(14):4232-4245

30. Qian J, Berkland C. (2015) pH-sensitive triblock copolymers for efficient siRNA encapsulation and delivery, Polymer Chemistry, 6(18):3472-3479

31. Fang WB, Yao M, Jokar I, Alhakamy N, Berkland C, Chen J, Brantley-Sieders D, Cheng N. (2015) The CCL2 chemokine is a negative regulator of autophagy and necrosis in luminal B breast cancer cells. Breast Cancer Research Treatment, 150(2):309-320

32.  W. Pornputtapitak, N. El-Gendy, and C. Berkland (2015) NanoCluster Itraconazole Formulations Provide a Potential Engineered Drug Particle Approach to Generate Effective Dry Powder Aerosols, Journal of Aerosol Medicine and Pulmonary Drug Delivery, 28(5):341-52

33.  Beck EC, Lohman B, Tabakh D, Kieweg SL, Gehrke SH, Berkland CJ, Detamore MS, (2015) Enabling surgical placement of hydrogels through achieving paste-like rheological behavior in hydrogel precursor solutions, Annals of Biomedical Engineering, 43(10):2569-76

34.  Hartwell BL, Antunez L, Sullivan BP, Thati S, Sestak JO, Berkland C. (2015) Multivalent Nanomaterials: Learning from Vaccines and Progressing to Antigen-Specific Immunotherapies. Journal of Pharmaceutical Science, 104(2):346-361

35.  Thati S, Kuehl C, Hartwell B, Sestak J, Siahaan T, Forrest L, Berkland C. (2015) Routes of Administration and Dose Optimization of Soluble Antigen Arrays in Mice with Experimental Autoimmune Encephalomyelitis. Journal of Pharmaceutical Science, 104(2):714-721

36.  Dennis SC, Bonewald L. Berkland C, Detamore MS (2014) Endochondral Ossification for Enhancing Bone Regeneration: Converging Native ECM Biomaterials and Developmental Engineering in vivo. Tissue Engineering Part B Reviews, 21(3):247-266

37.  Sestak JO, Fakhari A, Badawi AH, Siahaan TJ, Berkland C. (2014) Structure, size, and solubility of antigen arrays determines efficacy in experimental autoimmune encephalomyelitis. AAPS Journal Nov;16(6):1185-93.

38.  Northrup L, Sestak JO, Sullivan BP, Thati S, Hartwell BL, Siahaan TJ, Vines CM, Berkland C. (2014) Co-delivery of autoantigen and B7 pathway modulators suppresses experimental autoimmune encephalomyelitis. AAPS Journal Nov;16(6):1204-13.

39.  C. Kuehl, N. El-Gendy, and C. Berkland (2014) NanoClusters Surface Area Allows Nanoparticle Dissolution with Microparticle Properties. Journal of Pharmaceutical Sciences, 103(6):1787-1796

40.  S.C. Dennis, M.S. Detamore, S.L. Kieweg and C. Berkland (2014) Mapping Glycosaminoglycan-Hydroxyapatite Colloidal Gels as Potential Tissue Defect Fillers, Langmuir, 30(12):3528-3537

41.  A.A. Baoum, C.R. Middaugh and C. Berkland (2014) DNA complexed with TAT peptide and condensed using calcium possesses unique structural features compared to PEI polyplexes, International Journal of Pharmaceutics, 465(1-2):11-17

42.  J. Sestak, S. Thati, L. Northrup, M. Mullins, T.J. Siahaan, and C. Berkland (2014) Co-Delivery of Antigen and an Immune Cell adhesion Inhibitor is Necessary for Efficacy of Soluble Antigen Arrays in Experimental Encephalomyelitis, Molecular Therapy - Methods & Clinical Development, 1:14008

43.  W. Pornputtapitak, N. El-Gendy, J. Mermis, A. O'Brien-Ladner and C. Berkland (2014) NanoCluster budesonide formulations enable efficient drug delivery driven by mechanical ventilation, International Journal of Pharmaceutics, 462(1-2):19-28

44.  A. Fakhari, Q. Phan, and C. Berkland (2014) Hyaluronic acid colloidal gels as self-assembling elastic biomaterials, Journal of Biomedical Materials Research B, 102(3):612-618

45.  C. Chittasupho, J. Sestak, L. Shannon, T.J. Siahaan, C.M. Vines and C. Berkland (2014) Hyaluronic acid graft polymers displaying peptide antigen modulate dendritic cell response in vitro, Molecular Pharmaceutics, 11(1):367-373

46.  N.A. Alhakamy, A. Kaviratna, C.J. Berkland, and P. Dhar (2013) Dynamic measurements of membrane insertion potential of synthetic cell penetrating peptides, Langmuir, 29(49):15336-15349

47.   Q. Wang, Z. Gu, S. Jamal, M.S. Detamore MS, and C. Berkland (2013) Hybrid Hydroxyapatite Nanoparticle Colloidal Gels are Injectable Fillers for Bone Tissue Engineering, Tissue Engineering: Part A, 19(23-24):2586-2593

48.   N.H. Dormer, V. Gupta, A.M. Scurto, C.J. Berkland, and M.S. Detamore (2013) Effect of different sintering methods on bioactivity and release of proteins from PLGA microspheres, Materials Science and Engineering Part C, 33(7): 4343–4351, 2013.

49.   N.A. Alhakamy, A.S. Nigatu, C. Berkland, and J.D. Ramsey (2013) Noncovalently associated cell-penetrating peptides for gene delivery applications, Therapeutic Delivery, 4(6):741-757

50.   N.A El-Gendy, A. Kaviratna, C.J. Berkland, and P. Dhar (2013) Delivery and performance of surfactant replacement therapies to treat pulmonary disorders, Therapeutic Delivery, 4(8):951-980

51.   J. Sestak, S. Thati, L. Northrup, M. Mullins, T.J. Siahaan, and C. Berkland (2013) Single-Step Grafting of Aminooxy-Peptides to Hyaluronan: A Simple Approach to Multifunctional Therapeutics for Experimental Autoimmune Encephalomyelitis, Journal of Controlled Release, 168(3):334-340

52.   A. Fakhari, Q. Phan, and C. Berkland (2013) Hyaluronic acid nanoparticles titrate the viscoelastic properties of viscosupplements, Langmuir, 29(17):5123-5131

53.   A. Fakhari and C. Berkland (2013) Applications and Emerging Trends of Hyaluronic Acid in Tissue Engineering, as a Dermal Filler, and in Osteoarthritis Treatment, Acta Biomaterialia, 9(7):7081-7092

54.   N.A. Alhakamy and C. Berkland (2013) Polyarginine molecular weight determines transfection efficiency of calcium condensed complexes, Molecular Therapeutics, 10(5):1940-1948

55.   T.C. Suekama, V. Aziz, Z. Mohammadi, C. Berkland, S.H. Gehrke (2013) Synthesis and characterization of poly (N-vinyl formamide) hydrogels – A potential alternative to polyacrylamide hydrogels, Journal of Polymer Science Part A: Polymer Chemistry, 51:435-445

56.   S. Thaiboonrod, C. Berkland, A.H. Milani, R. Ulijn and Brian R. Saunders (2013) Poly(vinylamine) Microgels: pH-Responsive Particles with High Primary Amine Contents, Soft Matter, 9:3920-3930

57.   R. Phongpradist, S. Chiampanichayakul, S. Tima, T.J. Siahaan, C. Berkland, S. Anuchapreeda, and C. Ampasavate (2012) Potential cIBR-Conjugated PLGA Nanoparticles for Selective Targeting to Leukemic Cells, World Academy of Science, Engineering and Technology, 66:202-210

58.   J.H. Jeon, M. Bhamidipati, B. Sridharan, A.M. Scurto, C.J. Berkland, and M.S. Detamore (2012) Tailoring of processing parameters for sintering microsphere-based scaffolds with dense phase carbon dioxide, Journal of Biomedical Materials Research Part B, 101(2):330-337

59.   J. Yang, S.X. Xie, Y. Huang, M. Ling, J. Liu, Y. Ran, Y. Wang, J.B. Thrasher, C. Berkland, and B. Li (2012) Prostate-targeted biodegradable nanoparticles loaded with androgen receptor silencing constructs eradicate xenograft tumors in mice, Nanomedicine, 7(9):1297-309

60.   T.R. Bagby, S. Duan, S. Cai, S. Thati, C. Berkland, D. Aires and M.L. Forrest (2012) Lymphatic trafficking kinetics and near-infrared imaging using star polymer architectures with controlled anionic character, European Journal of Pharmaceutical Sciences, 47(1):287-294

61.   N. El-Gendy, P. Selvam, P. Soni and C. Berkland (2012) Development of Budesonide NanoCluster Dry Powder Aerosols: Processing, Journal of Pharmaceutical Sciences, 101(9):3425-3433

62.   N. El-Gendy, P. Selvam, P. Soni and C. Berkland (2012) Development of Budesonide NanoCluster Dry Powder Aerosols: Preformulation, Journal of Pharmaceutical Sciences, 101(9):3434-3444

63. N. El-Gendy, P. Selvam, P. Soni and C. Berkland (2012) Development of Budesonide NanoCluster Dry Powder Aerosols: Formulation and Stability, Journal of Pharmaceutical Sciences, 101(9):3445-3455

64. W. Pornputtapitak, N. El-Gendy, and C. Berkland (2012) Nanocluster budesonide formulations enhance drug delivery through endotracheal tubes, Journal of Pharmaceutical Sciences, 101(3):1063-1072

65. M.M. Bailey, S.R. Kline, M.D. Anderson, J.L. Staymates, C. Berkland (2012) Chemically Modifiable Fluorinated Copolymer Nanoparticles for 19F-MRI Contrast Enhancement, Journal of Applied Polymer Science, 126(4):1218-1227

66. A. Kawabata, A. Baoum, N. Ohta, S. Jacquez, G.M. Seo, C. Berkland, and M. Tamura (2012) Intratracheal administration of a nanoparticle-based therapy with the angiotensin II type 2 receptor gene attenuates lung cancer growth, Cancer Research, 72(8):2057-67

67. B. Buyuktimkin, Q. Wang, P. Kiptoo, J. Stewart, C. Berkland, and T. Siahaan (2012) Vaccine-like controlled-release delivery of an immunomodulating peptide to treat experimental autoimmune encephalomyelitis, Molecular Pharmaceutics, 9(4):979-985

68. Dormer NH, Berkland CJ, Detamore MS (2012) Osteogenic Differentiation of Human Bone Marrow Stromal Cells in Hydroxyapatite-Loaded Microsphere-Based Scaffolds, Tissue Engineering: Part A, 18(7-8):757-767

69. Baoum A, Ovachenkov D, and Berkland C (2012) Calcium Condensed Cell-Penetrating Peptide Complexes Offer Highly Efficient, Low Toxicity Gene Silencing, International Journal of Pharmaceutics, 427(1):134-142

70. Dormer NH, Berkland CJ, Detamore MS (2012) Osteochondral interface regeneration of the rabbit knee with macroscopic gradients of bioactive signals. Journal of Biomedical Materials Research: Part A, 100(1):162-170

71. S. Khondee, C. Olsen, Y. Zeng, C.R. Middaugh, and C. Berkland (2011) Non-covalent PEGylation by polyanion complexation as a means to stabilize keratinocyte growth factor-2 (KGF-2), Biomacromolecules, 12(11):3880-3894

72. N. El-Gendy, W. Pornputtapitak, and C. Berkland (2011) Nanoparticle agglomerates of fluticasone propionate in combination with albuterol sulfate as dry powder aerosols, European Journal of Pharmaceutics, 44(4):522-33

73. C. Chittasupho, T.J. Siahaan, C.M. Vines and C. Berkland (2011) Autoimmune therapies targeting costimulation and emerging trends in strategies using multivalent therapeutics, Therapeutic Delivery, 2(7):873-889

74. Lazebnik M, Singh M, Friis LA, Berkland CJ, Detamore MS (2011) Biomimetic method for combining the nucleus pulposus and annulus fibrosus for intervertebral disc tissue engineering, Journal of Tissue Engineering and Regenerative Medicine, 5(8): e179-e187

75. Dormer NH, Berkland CJ, Detamore MS (2011) Osteochondral interface regeneration of rabbit mandibular condyle with bioactive signal gradients. Journal of Oral Maxillofacial Surgery, 69(6):50-7

76. N. Mohan, V. Key, K.L. Caldwell, N. Dormer, C. Berkland and M.S. Detamore (2011) Continuous Gradients of Material Composition and Growth Factors for Effective Regeneration of the Osteochondral Interface, Tissue Engineering Part A, 17(21-22):2856-2855

77.   Q. Shang, X. Wang, M. Apley, S.B. Kukanich and C. Berkland (2011) PPF Microsphere Depot Sustains NSAID Blood Levels with Infusion-Like Kinetics without 'Burst', Journal of Veterinary Pharmacology and Therapeutics, 35(3):231-8

78.   Mohammadi Z, Xie S, Peltier E, Veisi M, Berkland C (2011) Enhancing the selectivity of an iron binding hydrogel, European Polymer Journal, European Polymer Journal, 47(7):1485-1488

79.   Khondee S, Baoum A, Siahaan, TJ, Berkland C (2011) Calcium Condensed LABL-TAT Complexes Effectively Target Gene Delivery to ICAM-1 Expressing Cells, Molecular Pharmaceutics, 8(3):788-98

80.   C. Chittasupho, L Shannon, J.P. Krise, TJ Siahaan, CM Vines and C. Berkland (2011) Nanoparticles targeting dendritic cell surface molecules effectively block T cell conjugation and shift response, ACS Nano, 5(3):1693-1702

81.   Mohammadi Z, Xie S, Allison G, Gehrke S and Berkland C (2011) Siderophore-Mimetic Hydrogel for Iron Chelation Therapy, Journal of Applied Polymer Science, 121(3):1384-1392

82.   Baoum A and Berkland C (2011) Calcium Condensation of DNA Complexed with Cell-Penetrating Peptides Offers Efficient, Noncytotoxic Gene Delivery, Journal of Pharmaceutical Sciences, 100(5):1637-1642

83.   Wang Q, Jamal S, Detamore MS, Berkland C (2011) PLGA-chitosan/PLGA-alginate nanoparticle blends as biodegradable colloidal gels for seeding human umbilical cord mesenchymal stem cells, Journal of Biomedical Materials Research, Part A 96(3):520-527

84.   Fakhari A, Baoum A, Siahaan TJ, Le KB, Berkland C (2011) Controlling ligand surface density optimizes nanoparticle binding to ICAM-1, Journal of Pharmaceutical Sciences, 100(3):1045-1056

85.   Janette Williams S, Huang HH, Kover K, Moore W, Berkland C, Singh M, Smirnova IV, Macgregor R, Stehno-Bittel L (2010) Reduction of diffusion barriers in isolated rat islets improves survival, but not insulin secretion or transplantation outcome, Organogenesis 6(2):115-24

86.   Aillon KL, El-Gendy N, Dennis C, Norenberg JP, McDonald J, Berkland C (2010) Iodinated NanoClusters as an inhaled computed tomography contrast agent for lung visualization, Molecular Pharmaceutics, 7(4):1274-1282

87.   Q. Wang, J. Wang, Q. Lu, M.S. Detamore and C. Berkland (2010) Injectable PLGA based colloidal gels for zero-order dexamethasone release in cranial defects, Biomaterials 31(18):4980-4986

88.   Dormer NH, Berkland CJ, Detamore MS (2010) Emerging techniques in stratified designs and continuous gradients for tissue engineering of interfaces. Annals of Biomedical Engineering, 38(6):2121-2141

89.   N. El-Gendy, K. Aillon and C. Berkland (2010) "Dry powdered aerosols of diatrizoic acid nanoparticle agglomerates as a lung contrast agent" International Journal of Pharmaceutics, 391(1-2):305-312

90.   Xie Y, Aillon KL, Cai S, Christian JM, Davies NM, Berkland CJ, Forrest ML (2010) Pulmonary delivery of cisplatin-hyaluronan conjugates via endotracheal instillation for the treatment of lung cancer. International Journal of Pharmaceutics, 392(1-2):156-163

91.   Dormer NH, Singh M, Wang L, Berkland CJ, Detamore MS (2010) Osteochondral interface tissue engineering using macroscopic gradients of bioactive signals. Annals of Biomedical Engineering, 38(6):2167-2182

92.   Phongpradist R, Chittasupho C, Okonogi S, Siahaan T, Anuchapreeda S, Ampasavate C, Berkland C (2010) LFA-1 on leukemic cells as a target for therapy or drug delivery. Current Pharmaceutical Design, 16(21):2321-2330

93.   M. Singh, N.H Dormer, M.S. Detamore and C. Berkland (2010) Three-dimensional Macroscopic Scaffolds With a Gradient in Stiffness for Functional Regeneration of Interfacial Tissues, Journal of Biomedical Materials Research: Part A 94(3):870-6

94.   Z. Mohammadi, X. Wang and C. Berkland (2010) "Magnetic Polyvinylamine Nanoparticles by In Situ Precipitation Reaction" The Journal of Polymer Science Part A: Polymer Chemistry 7(4):1274-1282

95.   L. Pickel, T. Matsuzuka, C. Doi, R. Ayuzawa, D.K. Maurya, S. Xie, C. Berkland and M. Tamura (2010) Overexpression of angiotensin II type 2 receptor gene induces cell death in lung adenocarcinoma cells, Cancer Biology & Therapy 9(4)

96.   C. Chittasupho, P. Manikwar, J.P. Krise, T. Siahaan and C. Berkland (2010) "cIBR effectively targets nanoparticles to LFA-1 on acute lymphoblastic T cells" Molecular Pharmaceutics 7(1):146-55

97.   A. Baoum, N. Dhillon, S. Buch and C. Berkland (2010) "Cationic surface modification of PLG nanoparticles offers sustained gene delivery to pulmonary epithelial cells" Journal of Pharmaceutical Sciences 99(5):2413-22

98.   M.M. Bailey, C.M. Mahoney, E. Dempah, J. Davis, M.L. Becker, S. Khondee, E.J. Munson, and C. Berkland (2010) "Fluorinated Copolymer Nanoparticles for Multimodal Imaging Applications;" Macromolecule Rapid Communications, 31(1):87-92

99.   S. Khondee, T. Yakovleva and C. Berkland (2010) " Low charge polyvinylamine nanogels offer sustained, low-level gene expression" Journal of Applied Polymer Science, 118(4):1921-1932

100. M. Singh, B. Sandhu, A. Scurto, C. Berkland and M.S. Detamore (2010) "Microsphere-Based Scaffolds for Cartilage Tissue Engineering: Using Subcritical $CO_2$ as a Sintering Agent" Acta Biomaterialia, 6:137-143

101. A. Baoum, S. Xie, and C. Berkland (2009) "'Soft' Calcium Crosslinks Enable Highly Efficient Gene Transfection Using TAT Peptide" Pharmaceutical Research, 26(12):2619-2629

102. M. Staymates, Fletcher R, Staymates J, Gillen G and Berkland C. (2009) Production and characterization of polymer microspheres containing trace explosives using precision particle fabrication technology, Journal of Microencapsulation 27(5):426-35

103. S.J. Johnson, J. Trejo, M. Veisi, G.P. Willhite, J.T. Liang, and C. Berkland (2009) "Effects of divalent cations, seawater, and formation brine on positively charged polyethylenimine/dextran sulfate/chromium(III) polyelectrolyte complexes and partially hydrolyzed polyacrylamide/chromium(III) gelation" Journal of Applied Polymer Science, 115(2):1008-1014

104. S.K. Nune, P. Gunda, P.K. Thallapally, Y.Y. Lin, M.L. Forrest, and C. Berkland (2009) "Nanoparticles for Biomedical Imaging" Expert Opinion on Drug Delivery, 6(11):1175-1194

105. S.J. Williams, Q. Wang, R.R. MacGregor, T.J. Siahaan, L. Stehno-Bittel and C. Berkland (2009) "Adhesion of Pancreatic Beta Cells to Biopolymer Films" Biopolymers, 91(8):676-685

106. N. El-Gendy and C. Berkland (2009) "Combination chemotherapeutic dry powder aerosols via controlled nanoparticle agglomeration" Pharmaceutical Research, 26(7):1752-1763

107. Z. Mohammadi, A. Cole and C. Berkland (2009) "In situ synthesis of iron oxide within polyvinylamine nanoparticle reactors" The Journal of Physical Chemistry Part C, 113(18):7652-7658

108. C. Chittasupho, S. Xie, A. Baoum, T. Yakovleva, T.J. Siahaan and C. Berkland (2009) "ICAM-1 Targeting of Doxorubicin-Loaded PLGA Nanoparticles to Lung Epithelial Cells" European Journal of Pharmaceutical Sciences, 37(2):141-150

109. K.L. Aillon, Y. Xie, N. El-Gendy, C. Berkland, and M.L. Forrest (2009) "Effects of nanomaterial physicochemical properties on in vivo toxicity" Advanced Drug Delivery Reviews, 61(6):457-466

110. C.J. Plumley, E. Gorman, C. Bybee E. Munson and C. Berkland (2009) "Nifedipine Nanoparticle Agglomeration as a Dry Powder Aerosol Formulation Strategy" International Journal of Pharmaceutics, 369(1-2):136-143

111. N. El-Gendy, E. Gorman, E. Munson and C. Berkland (2009) "Budesonide Nanoparticle Agglomerates as Dry Powder Aerosols with Rapid Dissolution" Journal of Pharmaceutical Sciences, 98(8):2731-2746

112. M. Bailey, E. Gorman, E. Munson and C. Berkland (2008) "Pure Insulin Nanoparticle Agglomerates for Pulmonary Delivery" Langmuir, 24(23):13641-13620

113. M. Bailey and C. Berkland (2008) "Nanoparticle Formulations in Pulmonary Drug Delivery" Medicinal Research Reviews, 29(1):196-212

114. M. Singh, C. Berkland and M.S. Detamore (2008) "Strategies and Applications for Incorporating Physical and Chemical Signal Gradients in Tissue Engineering" Tissue Engineering Part B, 14(4):341-366

115. M. Singh, C.P. Morris, R. Ellis, M.S. Detamore and C. Berkland (2008) "Microsphere-Based Seamless Scaffolds Containing Macroscopic Gradients of Encapsulated Factors for Tissue Engineering" Tissue Engineering Part C, 14(4):299-309

116. L. Shi, S. Khondee, T.H. Linz and C. Berkland (2008) "Poly(N-vinylformamide) Nanogels Capable of pH-Sensitive Protein Release" Macromolecules, 41(17):6546-6554

117. L.J. Peek, L. Roberts and C. Berkland (2008) "PLG Nanoparticle Agglomerates as Carriers in Dry Powder Aerosol Formulation of Proteins" Langmuir, 24(17):9775-9783

118. M. Cordova, M. Cheng, J., Trejo,S.J., Johnson, G.P. Willhite, J.T. Liang, and C. Berkland (2008) "Delayed HPAM Gelation via Transient Sequestration of Chromium in Polyelectrolyte Complex Nanoparticles" Macromolecules, 41(12):4398-4404

119. M. Huang and C. Berkland (2008) "Controlled Release of Repifermin® from Polyelectrolyte Complexes Stimulates Endothelial Cell Proliferation" Journal of Pharmaceutical Sciences, 98(1):268-280

120. M. Huang, Z.L. Huang, M. Bilgen and C. Berkland (2008) "MRI Contrast-Enhanced Polyelectrolyte Complexes" Nanomedicine, 4(1):30-40

121. L.J. Peek, C.R. Middaugh and C. Berkland (2008) "Nanotechnology in Vaccine Delivery" Advanced Drug Delivery Reviews, 60(8):915-28

122. N. Zhang, C. Chittasupho, C. Duangrat, T. Siahaan and C. Berkland (2008) "PLGA Nanoparticle-Peptide Conjugate Effectively Targets Intercellular Cell-Adhesion Molecule-1" Bioconjugate Chemistry, 19(1):145-152

123. Q. Wang, L. Wang, M. Detamore and C. Berkland (2008) "Biodegradable Colloidal Gels as Moldable Tissue Engineering Scaffolds" Advanced Materials, 20(2):236-239

124. L. Shi, C.J. Plumley and C. Berkland (2007) "Biodegradable Nanoparticle Flocculates for Dry Powder Aerosol Formulation" Langmuir, 23(22):10897-901

125. M.M. Arnold, E.M. Gorman, L.J. Scheiber, E.J. Munson and C. Berkland (2007) "NanoCipro Encapsulation in Monodisperse Large Porous PLGA Microparticles" Journal of Controlled Release, 120:100-109

126. M. Huang, S.N. Vitharana, L.J. Peek, T. Coop, and C. Berkland (2007) "Polyelectrolyte Complexes Stabilize and Controllably Release VEGF" Biomacromolecules, 8(5):1607-1614

127. L. Shi and C. Berkland (2007) "Acid-Labile Polyvinylamine Micro- and Nanogel Capsules" Macromolecules, 40(13):4635-4643

128. C. Berkland, E.J. Pollauf, C. Raman, R. Silverman, K. Kim, and D.W. Pack (2007) "Macromolecule release from monodisperse PLG microspheres: control of release rates and investigation of release mechanism" Journal of Pharmaceutical Sciences, 95(5):1176-1191

129. C. Berkland, E.J. Pollauf, N. Varde, D.W. Pack, and K. Kim (2007) "Monodisperse liquid-filled biodegradable microcapsules" Pharmaceutical Research, 24(5):1007-1013

130. L. Shi and C. Berkland (2006) "pH-Triggered Dispersion of Nanoparticle Clusters" Advanced Materials, 18(17):2315-2319

131. A.L. Dunehoo, M. Anderson, S. Majumdar, N. Kobayashi, C. Berkland and T.J. Siahaan (2006) "Cell adhesion molecules for targeted drug delivery" Journal of Pharmaceutical Sciences, 95(9):1856-1872

132. E.J. Pollauf, C. Berkland, K. Kim, and D.W. Pack (2005) "In vitro degradation of polyanhydride/polyester core-shell double-wall microspheres" International Journal of Pharmaceutics, 301(1-2):294-303

133. C. Raman, C. Berkland, K. Kim, and D.W. Pack (2005) "Modeling small-molecule release from PLG microspheres: effects of polymer degradation and non-uniform drug distribution" Journal of Controlled Release, 103(1):149-158

134. C. Berkland, K. Kim, and D.W. Pack (2004) "Three-month, zero-order piroxicam release from monodispersed double-walled microspheres of controlled shell thickness" Journal of Biomedical Materials Research 70A(4):576-584

135. C. Berkland, K. Kim, and D.W. Pack (2004) "Uniform double-walled polymer microspheres of controllable shell thickness" Journal of Controlled Release, 96(1):101-111

136. C. Berkland, K. Kim, and D.W. Pack (2004) "Controlling Surface Nano-Structure using Flow-Limited Field-Injection Electrostatic Spraying (FFESS) of Poly-(D,L-lactide-co-glycolide)." Biomaterials, 25(25):5649-58

137. C. Berkland, M.J. Kipper, B. Narasimhan, K. Kim, and D.W. Pack (2004) "Microsphere Size, Precipitation Kinetics, and Drug Distribution Control Drug Release from Biodegradable Polyanhydride Microspheres." Journal of Controlled Release, 94(1):129-141

138. C. Berkland, K. Kim, and D.W. Pack (2003) "PLG microsphere size controls drug release rate through several competing factors." Pharmaceutical Research, 20(7):1055-1062

139. C. Berkland, M. King, A. Cox, K. Kim, and D.W. Pack (2002) "Precise control of PLG microsphere size provides enhanced control of drug release rate." Journal of Controlled Release, 82(1):137-147

140. C. Berkland, K. Kim, and D.W. Pack (2001) "Fabrication of PLG microspheres with precisely controlled and monodisperse size distributions." Journal of Controlled Release, 73(1):59-74

## Non-Refereed Publications

141. G. Smaldone, I. Gonda, J. Mitchell, O. Usmani, C. Berkland, and A. Clark (2013) Ask the experts: The benefits and challenges of pulmonary drug delivery, Therapeutic Delivery 4(8):1-9

142. C. Berkland (2011) Engineering particles and colloids for pharmaceutical and biomaterial applications, Progress in Drug Delivery Systems XX, Shizuoka, Japan, 1-4

143. C. Berkland (2010) "Next Steps for Pharmaceutical Nanotechnology" Journal of Pharmaceutical Innovation 5(3):70-71

144. C. Berkland, G. Laurence, S. Lermer, P. Soni and M. Crowley (2010) "An overview of NanoCluster powder formulation technology" Pharmaceutical Technology 34(10):72-74,76,78

145. M. Bailey and C. Berkland (2010) "Research Spotlight: Therapeutic Particles and Biomaterials Technology Laboratory at The University of Kansas" Therapeutic Delivery 1(1):29-35

146. D.W. Pack, C. Berkland, N. Varde and K. Kim (2002) Precision polymer microshells for controlled-release drug delivery, 223rd ACS National Meeting extended abstract

147. C. Berkland, K. Kim and D. Pack (2000) Fabrication of PLGA microspheres with precisely controlled, homogeneous size distribution, Proceedings of the International Symposium on Controlled Release of Bioactive Materials, 1130-1131

## Book Chapters

1.   N. El-Gendy, M. Bailey and C. Berkland (2014) "Particle Engineering Technologies for Pulmonary Drug Delivery" Controlled Release Science and Technology: Pulmonary Delivery, Ed. Hugh Smyth and Anthony Hickey, 283-312

2.   N.H. Dormer, C.J. Berkland and M. Singh (2014) "Monodispersed Microencapsulation Technology" Microencapsulation in the Food Industry, Ed. N. Vasisht, A.R. Khare and R. Sobel

3.   M. Bailey and C. Berkland (2010) "Modified release delivery systems" Biodrug Delivery Systems, Vol. 194, Ed. Mariko Morishita and Kinam Park, 234-247

## Invited Presentations

1.   C. Berkland "Soluble antigen arrays as antigen-specific autoimmune therapy" Globalization of Pharmaceutics Education Network, Lawrence, Kansas, November 12, 2016

2.   C. Berkland "Entrepreneurship: Intellectual Property Strategy" Globalization of Pharmaceutics Education Network, Lawrence, Kansas, November 12, 2016

3.   C. Berkland "A few early lessons in entrepreneurship", Chemical and Biomolecular Engineering Department, The University of Illinois, Urbana-Champaign, IL, October 23, 2016

4.   C. Berkland "A discussion of venture capital and the role of scientists", The University of Texas, Austin, TX, September 29, 2016

5.   C. Berkland "Biomaterials and Controlled Release in Bone Tissue Engineering", The University of Kansas Medical Center, Kansas City, KS, June 15, 2016

6.   C. Berkland "Early Lessons in Entrepreneurship: A Venture Capital Perspective", American Thoracic Society, San Francisco, CA, September 15, 2016

7.   C. Berkland "Drug delivery systems for improving ocular therapeutics", Allergan, Irvine, CA, June 2, 2016

8.   C. Berkland "Barriers to effective gene delivery", Cystic Fibrosis Foundation Pushing the Frontiers workshop, Chantilly, VA, June 3, 2015

9.   C. Berkland "Polyelectrolyte complexes for gene delivery to lungs", Cystic Fibrosis Foundation Therapeutics Gene Repair and Delivery workshop, Cystic Fibrosis Foundation, Bethesda, MD, December 3, 2014

10. C. Berkland "A few early lessons in entrepreneurship", Bioengineering Department, The University of California, Berkeley, CA, October 15, 2014

11. C. Berkland "Controlled release delivery of proteins" Genentech, South San Francisco, California, December 21, 2014

12. C. Berkland "A few early lessons in entrepreneurship", Chemistry Department, The University of Kansas, Lawrence, KS, February 19, 2014

13. C. Berkland "Translatable Pharmaceutical Formulations of Aerosolized and Topical Antibiotics", U.S. Army Medical Research Institute of Infectious Diseases, Fort Detrick, MD, February 18, 2014

14. C. Berkland "A few early lessons in entrepreneurship", Chemical and Biomolecular Engineering Department 100 year Anniversary Symposium, Iowa State University, Ames, IA, September 27, 2013

15. J. Sestak, S. Thati, L. Northrup, M. Mullins, T.J. Siahaan, and C. Berkland "Single-Step Grafting of Aminooxy-Peptides to Hyaluronan: A Simple Approach to Multifunctional Therapeutics for Experimental Autoimmune Encephalomyelitis", ACS annual meeting, Indianapolis, Indiana, September 9, 2013

16. C. Berkland "Precision Particle Fabrication", ACS annual meeting, Indianapolis, Indiana, September 9, 2013

17. C. Berkland "Designing formulation and delivery with drug properties in mind", Gordon Conference: Preclinical Form and Formulation for Drug Discovery, Waterville Valley, New Hampshire, June 5, 2013

18. C. Berkland "Colloids and polymers for chemical delivery", Iowa State University, Ames, IA, April 19, 2013

19. S.C. Dennis, Q. Wang, S. Kieweg, M.S. Detamore and C.J. Berkland "Colloidal Gels as a New Class of 'Bingham Plastic' Biomaterials for Tissue Regeneration", CMBE annual meeting, Kohala Coast, Hawaii, January 6, 2013

20. C. Berkland "Colloids and polymers for drug and chemical delivery", Kansas State University, Manhattan, Kansas, November 5, 2012

21. C. Berkland "Uniform PLGA Microspheres Sustain NSAID Blood Levels With Zero-Order Kinetics", Controlled Release Society Annual Meeting, Quebec, Canada, July 16, 2012

22. C. Berkland "Personal and Professional Experiences in Controlled Release", Controlled Release Society Annual Meeting Young Investigator Award Presentation, Quebec, Canada, July 16, 2012

23. C. Berkland "Advanced Materials and Drug Delivery", Kimberly-Clark Heritage Lecture Series, Atlanta, Georgia, May 31, 2012

24. C. Berkland "Colloids and polymers for chemical delivery", Program of Excellence in Nanotechnology lecture series at MIT, Cambridge, Massachusetts, April 25, 2012

25. C. Berkland "Precision Particle Fabrication" Reckitt Benckiser, Hull, United Kingdom, April 11, 2012

26. C. Berkland "Precision Particle Fabrication" Kimberly-Clark, Atlanta, Georgia, April 4, 2012

27. C. Berkland "Precision Particle Fabrication" Dow Chemical, Midland, Michigan, December 7, 2011

28. J. Liang and C. Berkland "Polyelectrolyte complexes for oil and gas field applications" Schlumberger, Houston, Texas, November 14, 2011

29. C. Berkland "Engineering particles and colloids for pharmaceutical and biomaterial applications" Nagai Foundation Distinguished Lectureship for the Annual DDS Conference, Shizouka, Japan, September 15, 2011 (Keynote address)

30. C. Berkland "Nanoparticle Aerosol Formulations for Delivery of Current Drugs and Emerging Nucleic Acid Therapeutics" Defense Threat Reduction Agency, Washington D.C., August 1, 2011

31. C. Berkland "Regenerative Nanomaterials" Kinetic Concepts, Inc., San Antonio, Texas, July 11, 2011

32. C. Berkland "NanoCluster Technology and Microcapsule Approaches for Improved Dissolution and Solubilization" IQPC Improving Solubility Conference, Philadelphia, Pennsylvania, March 29, 2011

33. C. Berkland "Precision Particle Fabrication" Bioencapsulation Industrial Symposium, San Antonio, Texas, March 8, 2011

34. C. Berkland "Approaches for Synthesis, Formulation and Targeting of Various Contrast-Enhancing Colloids" General Electric Research Center, Albany, New York, January 6, 2011

35. C. Berkland "Targeted Nanomaterial Therapeutics" University of Pennsylvania, Philadelphia, Pennsylvania, January 7, 2011

36. C. Berkland "NanoClusters as Unique High Performance Aerosols" MAP Pharmaceuticals, South San Francisco, California, December 21, 2010

37. C. Berkland "Precision Particle Fabrication" Genentech, South San Francisco, California, December 21, 2010

38. C. Berkland "Colloids Engineered for Drug Delivery and Biomaterials Applications" University of Geneva, Geneva, Switzerland, October 22, 2010

39. C. Berkland "Engineering Particles: Microencapsulation and Advanced Nanoparticle Colloids" Jannsen Pharmaceuticals, Beerse, Belgium, October 21, 2010

40. C. Berkland "Colloids Engineered for Drug Delivery and Biomaterials Applications" Eidgenössische Technische Hochschule, Zürich, Switzerland, October 19, 2010

41. C. Berkland "NanoClusters as Unique High Performance Aerosols" Nycomed, Konstanz, Germany, October 18, 2010

42. C. Berkland "Precision Particles for Controlled Release" Genentech, South San Francisco, California, September 21, 2010

43. C. Berkland "NanoCluster Formulation Technology" Novartis, South San Francisco, California, July 27, 2010

44. C. Berkland "Nanoparticle Formulation Approaches in Injectable and Pulmonary Medicines" The University of Missouri, Kansas City, Missouri, American Association of Pharmaceutical Scientists Student Chapter Distinguished Lecturer Series, May 26, 2009

45. C. Berkland "Particle Engineering in Aerosol and Injectable Formulations" The University of Wisconsin, Madison, Wisconsin, February 27, 2009

46. C. Berkland "Nanoparticles in Pulmonary Medicine" The University of Kansas Medical Center, Division of Pulmonary and Critical Care Medicine, Kansas City, Kansas, October 21, 2008

47. C. Berkland "Particle Engineering in Inhaled and Injectable Drug Formulations" Genentech, South San Francisco, California, July 30, 2008

48. J. Liang, P. Willhite and C. Berkland "Nanotechnology: From Drugs to Oil Refining" 3M Technical Forum, Minneapolis, Minnesota, June 26, 2008

49. C. Berkland "Translating Therapeutic Nanoparticles" Particles 2008, Orlando, Florida, May 11, 2008

50. C. Berkland "Pharmaceutical Applications of Nanoparticle Technology" Cima Labs, Brooklyn Park, Minnesota, August 27, 2007

51. C. Berkland "Engineering Nanoparticles for Biomedicine" National Institute of Standards and Technology, Gaithersburg, Maryland, May 4, 2007

52. M. Cordova, M. Cheng, P.G. Willhite, J. Liang, and C. Berkland "Polyelectrolyte complexes for oil and gas field applications" Conoco Phillips, Bartlesville, Oklahoma, March 13, 2007

53. C. Berkland "Nanoparticles for Targeted Angiogenesis: Potential Applications in Heart Disease and Spinal Cord Injury" Genentech, South San Francisco, California, November 14, 2006

54. C. Berkland "Engineering Pharmaceutical Nanoparticles" Globalization of Pharmaceutics Education Network, Lawrence, Kansas, October 26, 2006

55. C. Berkland "Nanoparticle Agglomeration for Dry Powder Formulation" Schering Plough's Pharmaceutical Science Seminar Series in Product Development, Kenilworth, New Jersey, September 27, 2006

56. C. Berkland "Nanoparticle Technology in the Pharmaceutical Industry" AAPS Kansas City Discussion Group, Kansas City, Kansas, August 8, 2006

57. C. Berkland "Nanoclusters as a Unique Drug Delivery Platform" ACS Particles Meeting, Orlando, Florida, May 16, 2006

58. C. Berkland "Designing Particulate Vaccine Delivery Systems" Mannkind Corporation, Valencia, California, January 24, 2006

59. C. Berkland "Precision Particle Fabrication Technology" Southwest Research Institute, San Antonio, Texas, January 11, 2006

60. C. Berkland "Engineering Therapeutic Particles" guest lecturer in senior Biochemical Engineering course at Vanderbilt University, Nashville, Tennessee, November 7, 2005

61. C. Berkland "API Particle Engineering" 47th Annual International Industrial Pharmaceutical Research & Development Conference: Emerging Practices for Advancing Drug Development, Merrimac, Wisconsin, June 7, 2005

62. C. Berkland "Engineering micro- and nanoparticles for enhanced drug delivery performance" University of Kansas, Department of Chemistry, Lawrence, Kansas, March 7, 2005

63. C. Berkland "Improvements in Delivery Strategies Using Particulate Technologies to Treat Infectious Diseases" 3rd Annual Great Plains Infectious Disease Meeting, Lawrence, Kansas, September 18, 2004

## Thesis Advisor and Postgraduate-Scholar Sponsor

Graduate students
Sam Peterson, Pharmaceutical Chemistry
Melissa Pressnall, Pharmaceutical Chemistry
Jimmy Song, Pharmaceutical Chemistry
Martin Leon, Chemistry
Jonathan Daniel Griffin, Bioengineering
Matthew Christopher, Pharmaceutical Chemistry
Chad Pickens, Pharmaceutical Chemistry
Lorena Antunez, Pharmaceutical Chemistry
Brittany Rover, Bioengineering
Laura Northrup, Pharmaceutical Chemistry
Christopher Kuehl, Pharmaceutical Chemistry
Sharadvi Thati, Pharmaceutical Chemistry
Connor Dennis, Bioengineering
Adel Alghaith, Pharmaceutical Chemistry
Nabil Alhakamy, Pharmaceutical Chemistry
Warangkana Pornputtapitak, Pharmaceutical Chemistry
Auan Rungisee, Chiang Mai University visiting
Abdul Baoum, Pharmaceutical Chemistry
Qun Wang, Chemical Engineering
Milind Singh (co-advisor with Michael Detamore), Chemical Engineering
Mark Bailey, Bioengineering
Carl Plumley, Chemical Engineering
Zahra Mohammdi, Chemical Engineering
Chuda Chittasupho, Pharmaceutical Chemistry
Supang Khondee, Pharmaceutical Chemistry
Joshua Sestak, Pharmaceutical Chemistry
Amir Fakhari, Bioengineering
Matthew Arnold, Chemical Engineering

Postdoc sponsor
Sharadvi Thati, KU, Lawrence
Madhuri Patil, KU, Lawrence
Bradly Sullivan, KU, Lawrence
Ola Alawode, KU. Lawrence
Jun Chen, KU, Lawrence
Jian Qian, KU, Lawrence
Joshua Sestak, KU, Lawrence
Xiang Wang, KU, Lawrence
Qing Shang, KU, Lawrence
Nashwa El Gendy, KU, Lawrence
Sheng-Xue Xie, KU, Lawrence

Tatyana Yakovleva, KU, Lawrence
Huili Guan, KU, Lawrence
Kristin Aillen, KU, Lawrence
Julieta Trejo, KU, Lawrence (co-advised with Paul Willhite and Jenn-Tai Liang)
Stephen Johnson, KU, Lawrence (co-advised with Paul Willhite and Jenn-Tai Liang)
Ying Ying Lin, KU, Lawrence (co-advised with Paul Willhite and Jenn-Tai Liang)
Parthiban Selvam, KU, Lawrence
Yasunori Iwao, University of Shizuoka, Japan
Satish Nune, KU, KU, Lawrence
Navneet Dhillon, KU Medical Center, Kansas City (co-advised with Shilpa Buch)
Lianjun Shi, KU, Lawrence
Min Huang, KU, Lawrence
Laura Peek, KU, Lawrence
Samadhi Vitharana, KU, Lawrence
Na Zhang, Associate Professor, Shandong University, China
Chadarat Duangrat, Assistant Professor, Chiang Mai University, Thailand

## Teaching Experience

| | |
|---|---|
| Pharmaceutical Chemistry<br>PHCH 510 Emerging Trends in Pharmaceutical Chemistry | Fall 2006<br>Fall 2008<br>Fall 2010<br>Fall 2012<br>Fall 2016 |
| Chemical Engineering/Pharmaceutical Chemistry<br>CPE/PHCH 715 Drug Delivery<br>Coordinated and taught a new graduate-level course in drug delivery principles. | Fall 2005<br>Fall 2007<br>Fall 2009<br>Fall 2011<br>Fall 2013<br>Spring 2016<br>Spring 2017 |
| Pharmaceutical Chemistry<br>PHCH 626 Biopharmaceutics and Drug Delivery | Spring 2016 |
| Chemical Engineering<br>CPE 221 Introduction to Thermodynamics | Spring 2008<br>Spring 2009<br>Spring 2010 |
| Chemical Engineering<br>CPE 111 Introduction to Chemical Engineering | Fall 2006 |
| Chemical Engineering<br>CPE 800 Graduate Seminar | Fall 2006 |
| Chemical Engineering<br>CPE 732 Advanced Transport Phenomena II<br>Coordinated and taught the mass transport course to graduate students. | Spring 2005<br>Spring 2006<br>Spring 2007 |

## Teaching Recognition

W.T. Kemper Fellowship for Teaching Excellence (2010)

C&PE 656 Introduction to Biomedical Engineering (2006)

 Received second most votes for "best teacher" and for "most interesting topic" out of 12 guest lecturers for C&PE 656. Two of these lecturers were Kemper Award winners.

Teaching Achievement Award from CPE graduate students at the CTE Celebration of Teaching (2007)

C&PE 656 Introduction to Biomedical Engineering (2008)

 Received most votes for "best teacher" and second most for "most interesting topic" out of 12 guest lecturers for C&PE 656.


## Professional Activities

Co-founder, Board Member and acting CSO of Orbis Biosciences, Inc.
Co-founder, Scientific Advisory Board Member and prior CTO of Savara Pharmaceuticals, Inc.
Co-founder, Chairman of the Board of Orion BioScience, Inc.
Co-founder, Board Member and acting CSO, Bond Biosciences, Inc.

Cystic Fibrosis Foundation Workshop panel to determine funding directives (2014)

NIH Study Sections: NHLBI Programs of Excellence in Nanotechnology, NIAID B cell Immunology Program, ETTN special emphasis on pediatric medicine, NANO

Training grants –  Advisory Board; NIH NIAID – Multidimensional Vacinogenesis (past)
     Advisory Board; NIH NIGMS – Pharmaceutical Aspects of Biotechnology

Journal Advisory Boards – Journal of Pharmaceutical Sciences (2008-present)
      Journal of Pharmaceutical Innovation (2008-present)
      Therapeutic Delivery (2009-2015)

Academic Advisory Boards – Kansas University Innovation Center, The University of Kansas
      D3ET Research Program Steering Committee, The University of Kansas
      KU Strategic Initiative Committee "Promoting Well-Being, Finding Cures"

Corporate Advising – Banner Life Sciences (2015-present)
      Dauntless Pharmaceuticals (2015-2016)

Lawrence High School, Lawrence, KS – Technology Department Advisory Board (2006-2012). Served to develop/improve curriculum for pre-engineering training of local junior high and high schools.

Education –   Director – Pharmaceutical Chemistry Undergraduate Research Program (2006-present)
     Director – Education through Outreach with Lawrence High School (NSF sponsored). More than 25 high school students have conducted research at KU through this program. (2008-2013)
     Director – Biomolecular Engineering Track, BioEngineering Program at KU (2010-2015)
     Drug Delivery; New graduate course offering at KU
     Chemical Engineering; Module for College Prep Engineering at Lawrence High School
     Short course "Polymers in Drug delivery: Nanocarriers and implantable polymeric drug delivery systems" Globalization of Pharmaceutics Education Network, Lawrence, KS
     Short course "Polymers in Drug delivery: Nanocarriers and implantable polymeric drug delivery systems" Globalization of Pharmaceutics Education Network, Lawrence, KS